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【発明の名称】 新規ベンズアミド誘導体

【請求項の数】 6

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【物件名】 明細書　1

【物件名】 図面　1

【物件名】 要約書　1

【プルーフの要否】 不要

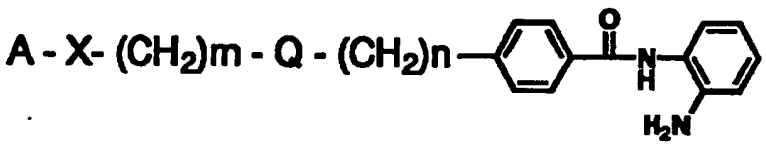
【書類名】　明細書

【発明の名称】新規ベンズアミド誘導体

【特許請求の範囲】

【請求項１】　一般式（１）［化１］

【化１】



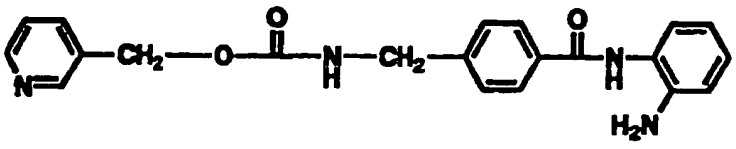
(1)

［式中、Ａは置換されていてもよいフェニル基または複素環（置換基として、ハロゲン原子、水酸基、アミノ基、ニトロ基、シアノ基、炭素数１から４のアルキル基、炭素数１から４のアルコキシ基、炭素数１から４のアミノアルキル基、炭素数１から４のアルキルアミノ基、炭素数１から４のアシル基、炭素数１から４のアシルアミノ基、炭素数１から４のアルキルチオ基、炭素数１から４のパーフルオロアルキル基、炭素数１から４のパーフルオロアルキルオキシ基、カルボキシル基、炭素数１から４のアルコキシカルボニル基、フェニル基、複素環からなる群より選ばれた基を１から４個有する）を表す。Ｘは直接結合、－Ｏ－、－Ｓ－または－ＮＨ－を表す。ｍ及びｎはそれぞれ独立して０から４の整数を表す。但し、ｍとｎは同時に０とはならない。Ｑはアミド結合、チオアミド結合、ウレタン結合、チオウレタン結合、ウレア結合、チオウレア結合のいずれかを表す。］で表されるベンズアミド誘導体またはその薬学的に許容される塩。

【請求項２】　Ａが置換されていてもよいピリジル基である請求項１記載のベンズアミド誘導体またはその薬学的に許容される塩。

【請求項３】　式（２）［化２］

【化２】

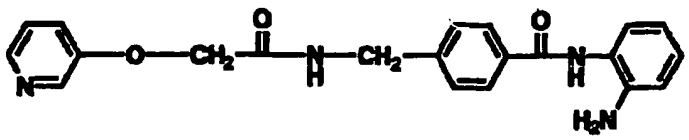


(2)

で示される請求項１記載のベンズアミド誘導体またはその薬学的に許容される塩

【請求項４】 式（３）［化３］

【化３】



(3)

で示される請求項１記載のベンズアミド誘導体またはその薬学的に許容される塩。

【請求項５】 請求項１から４のいずれかに記載の化合物のうち、少なくとも１つを有効成分として含有する制癌剤。

【請求項６】 請求項１から４のいずれかに記載の化合物のうち、少なくとも１つを有効成分として含有する医薬品。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は新規なベンズアミド誘導体に関する。さらに詳しくは、新規ベンズアミド誘導体の分化誘導作用に基づく制癌剤およびその他の医薬品への利用に関するものである。

【０００２】

【従来の技術】現在、癌は死亡原因の中で心疾患、脳血管疾患を抜いて最大の原因となっており、これまで多くの研究が多額の費用と時間をかけて行われてきた。しかし、外科的手術、放射線療法、温熱療法など多岐にわたる治療法の研究にも拘らず癌は克服されていない。その中で化学療法は癌治療の大きな柱の一つであるが、今日に至っても十分満足のゆく薬剤は見いだされておらず、毒性が低く治療効果の高い制癌剤が待ち望まれている。これまでの多くの制癌剤は細胞、主にＤＮＡに作用し細胞毒性を発現することで癌細胞に傷害を与え、制癌効果を発揮している。しかし、癌細胞と正常細胞との選択性が十分でないため、正常細胞において発現する副作用が治療の限界となっている。

【０００３】

ところが制癌剤の中でも分化誘導剤は直接の殺細胞ではなく、癌細胞に分化を促し癌細胞の無限増殖を抑えることを目的としている。そのため癌の退縮におい

ては直接細胞を殺す種類の制癌剤には及ばないが、低い毒性と異なる選択性が期待できる。実際、分化誘導剤であるレチノイン酸が治療に用いられ急性前骨髄性白血病で高い効果を示すことはよく知られている［Ｈｕａｎｇら；Ｂｌｏｏｄ、７２、５６７－５７２（１９８８）、Ｃａｓｔａｉｇｎら；Ｂｌｏｏｄ、７６、１７０４－１７０９、（１９９０）あるいはＷａｒｒｅｌｌら；Ｎｅｗ Ｅｎｇｌ．Ｊ．Ｍｅｄ．３２４、１３８５－１３９３（１９９１）など］。また、ビタミンＤ誘導体が分化誘導作用を示すことから制癌剤への応用も多く研究されている［Ｏｌｓｓｏｎら；Ｃａｎｃｅｒ Ｒｅｓ．４３、５８６２－５８６７（１９８３）他］。

【０００４】

これらの研究を受けて、分化誘導剤であるビタミンＤ誘導体（特開平６－１７９６２２号公報）、イソプレン誘導体（特開平６－１９２０７３号公報）、トコフェロール（特開平６－２５６１８１号公報）、キノン誘導体（特開平６－３０５９５５号公報）、非環状ポリイソプレノイド（特開平６－３１６５２０号公報）、安息香酸誘導体（特開平７－２０６７６５号公報）、糖脂質（特開平７－２５８１００号公報）等の制癌剤への応用が報告されている。しかしながら、これらの研究によっても癌治療上十分なレベルに達した薬剤はなく、各種の癌に対し有効で安全性の高い薬剤が強く望まれている。

【０００５】

【発明が解決しようとする課題】本発明の課題は、分化誘導作用を有し、悪性腫瘍、自己免疫疾患、皮膚病の治療・改善薬などの医薬品として有用な化合物を提供することにある。

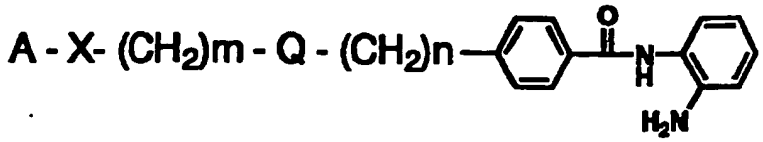
【０００６】

【課題を解決するための手段】本発明者は上記課題を解決すべく鋭意検討した結果、分化誘導作用を有する新規ベンズアミド誘導体が抗腫瘍効果を示すことを見いだし、本発明を完成させた。すなわち本発明は、

［１］　一般式（１）［化４］

【０００７】

【化４】



(1)

［式中、Ａは置換されていてもよいフェニル基または複素環（置換基として、ハロゲン原子、水酸基、アミノ基、ニトロ基、シアノ基、炭素数１から４のアルキル基、炭素数１から４のアルコキシ基、炭素数１から４のアミノアルキル基、炭素数１から４のアルキルアミノ基、炭素数１から４のアシル基、炭素数１から４のアシルアミノ基、炭素数１から４のアルキルチオ基、炭素数１から４のパーフルオロアルキル基、炭素数１から４のパーフルオロアルキルオキシ基、カルボキシル基、炭素数１から４のアルコキシカルボニル基、フェニル基、複素環からなる群より選ばれた基を１から４個有する）を表す。Ｘは直接結合、－Ｏ－、－Ｓ－または－ＮＨ－を表す。ｍ及びｎはそれぞれ独立して０から４の整数を表す。但し、ｍとｎは同時に０とはならない。Ｑはアミド結合、チオアミド結合、ウレタン結合、チオウレタン結合、ウレア結合、チオウレア結合のいずれかを表す。］で表されるベンズアミド誘導体またはその薬学的に許容される塩であり、また、

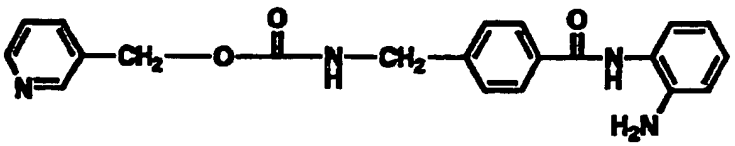
【０００８】

［２］　Ａが置換されていてもよいピリジル基である［１］記載のベンズアミド誘導体またはその薬学的に許容される塩であり、また、

［３］　式（２）［化５］

【０００９】

【化５】



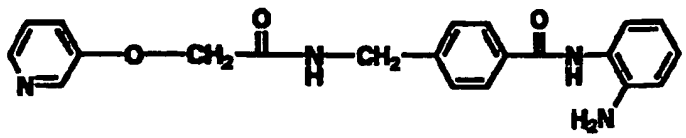
(2)

で示される［１］記載のベンズアミド誘導体またはその薬学的に許容される塩であり、また、

［４］　式（３）［化６］

【００１０】

【化６】



(3)

で示される［１］記載のベンズアミド誘導体またはその薬学的に許容される塩であり、また、

【００１１】

［５］　［１］から［４］のいずれかに記載の化合物のうち、少なくとも１つを有効成分として含有する制癌剤であり、また、

【００１２】

［６］　［１］から［４］のいずれかに記載の化合物のうち、少なくとも１つを有効成分として含有する医薬品である。

【００１３】

【発明の実施の形態】

以下、本発明を詳細に説明する。

本発明でいう炭素数１から４とは、単位置換基あたりの炭素数を表す。すなわちジアルキル置換の場合は、炭素数２から８を意味する。

一般式（１）で示される化合物における複素環とは、窒素原子または酸素原子または硫黄原子を１から４個を含む５員環または６員環で、例えばピリジン、ピラジン、ピリミジン、ピリダジン、チオフェン、フラン、ピロール、ピラゾール、イソオキサゾール、イソチアゾール、イミダゾール、オキサゾール、チアゾール、ピペリジン、ピペラジン、ピロリジン、キヌクリジン、テトラヒドロフラン、モルホリン、チオモルホリンなどを挙げることができる。

【００１４】

ハロゲン原子とは、フッ素原子、塩素原子、臭素原子、ヨウ素原子を挙げることができる。

炭素数１から４のアルキル基とは、例えばメチル基、エチル基、ｎ－プロピル基、イソプロピル基、ｎ－ブチル基、イソブチル基、ｓｅｃ－ブチル基、ｔｅｒｔ－ブチル基などを挙げることができる。

【００１５】

炭素数１から４のアルコキシ基とは、例えばメトキシ基、エトキシ基、ｎ－プロポキシ基、イソプロポキシ基、アリルオキシ基、ｎ－ブトキシ基、イソブトキシ基、ｓｅｃ－ブトキシ基、ｔｅｒｔ－ブトキシ基などを挙げることができる。

炭素数１から４のアミノアルキル基とは、例えばアミノメチル基、１－アミノエチル基、２－アミノプロピル基などを挙げることができる。

【００１６】

炭素数１から４のアルキルアミノ基とは、例えばＮ－メチルアミノ基、Ｎ，Ｎ－ジメチルアミノ基、Ｎ，Ｎ－ジエチルアミノ基、Ｎ－メチル－Ｎ－エチルアミノ基、Ｎ，Ｎ－ジイソプロピルアミノ基などを挙げることができる。

炭素数１から４のアシル基とは、例えばアセチル基、プロパノイル基、ブタノイル基を挙げることができる。

【００１７】

炭素数１から４のアシルアミノ基とは、例えばアセチルアミノ基、プロパノイルアミノ基、ブタノイルアミノ基などを挙げることができる。

炭素数１から４のアルキルチオ基とは、メチルチオ基、エチルチオ基、プロピルチオ基などを挙げることができる。

炭素数１から４のパーフルオロアルキル基とは、例えばトリフルオロメチル基、ペンタフルオロエチル基などを挙げることができる。

【００１８】

炭素数１から４のパーフルオロアルキルオキシ基とは、例えばトリフルオロメトキシ基、ペンタフルオロエトキシ基などを挙げることができる。

炭素数１から４のアルコキシカルボニル基とは、例えばメトキシカルボニル基、エトキシカルボニル基などを挙げることができる。

薬学的に許容される化合物の塩とは、この分野で常用される塩酸、臭化水素酸、硫酸、燐酸などの無機酸や、酢酸、酒石酸、フマル酸、マレイン酸、クエン酸、安息香酸、トリフルオロ酢酸、ｐ－トルエンスルホン酸などの有機酸との塩を挙げることができる。

請求項６にいう医薬品とは、制癌剤または自己免疫疾患、皮膚病などの治療・

改善薬を表す。

一般式（1）においてAに不斉炭素を有する場合は、異なった立体異性形態またはラセミ形態を含む立体異性形態の混合物の形態で存在することができる。すなわち、本発明はこのように規定した種々の形態をも包含するが、これらも同様に有効成分化合物として用いることができる。

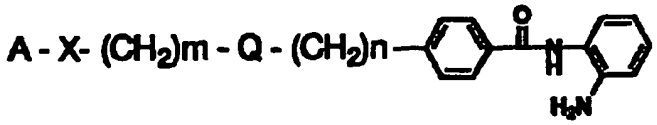
【0019】

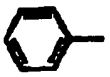
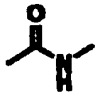
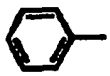
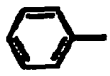
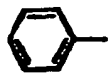
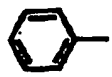
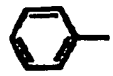
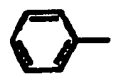
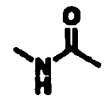
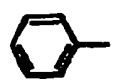
以下、本発明の一般式（1）で示される代表的化合物を表－1［表1－表16］に具体的に例示する。なお、本発明はこれらの例に限定されるものではない。

【００２０】

【表１】

表－１

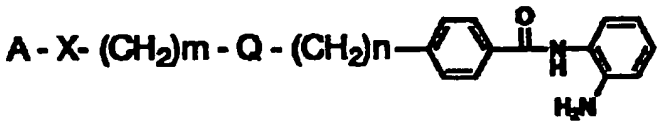


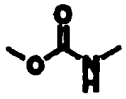
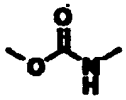
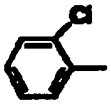
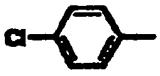
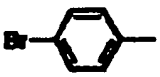
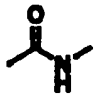
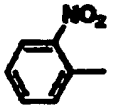
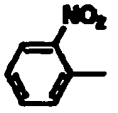
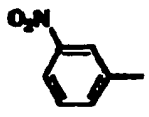
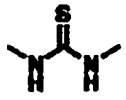
化合物番号	A	X	m	Q	n
1		直接結合	0		1
2		直接結合	1		0
3		直接結合	2		0
4		直接結合	3		0
5		直接結合	4		0
6		直接結合	1		1
7		直接結合	2		1
8		直接結合	1		0
9		直接結合	2		0
10		直接結合	0		1

【0021】

【表2】

表－1続きの1

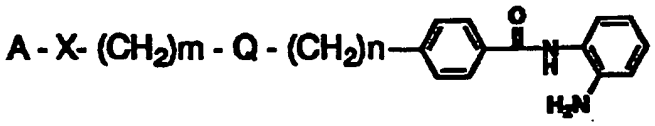


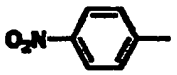
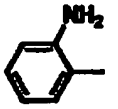
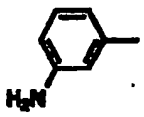
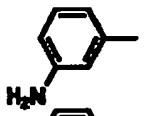
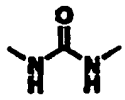
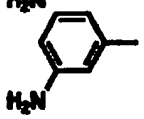
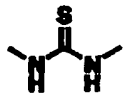
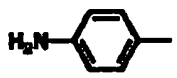
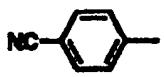
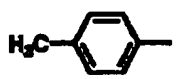
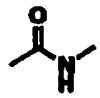
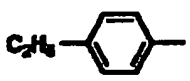
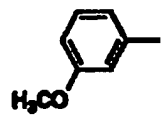
化合物番号	A	X	m	Q	n
11		直接結合	1		1
12		直接結合	0		1
13		直接結合	0		1
14		直接結合	0		1
15		直接結合	1		0
16		直接結合	0		1
17		直接結合	0		1
18		直接結合	0		1
19		直接結合	1		0
20		直接結合	0		1

【0022】

【表3】

表－1続きの2

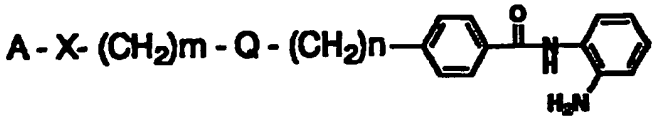


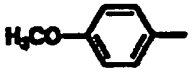
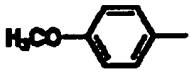
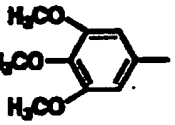
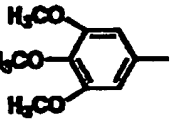
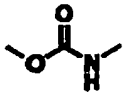
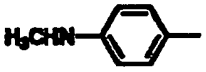
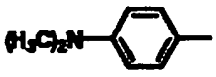
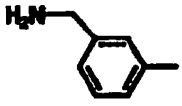
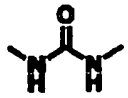
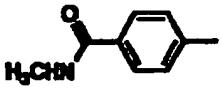
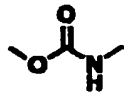
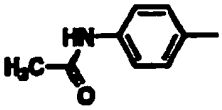
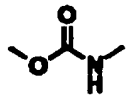
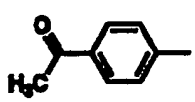
化合物番号	A	X	m	Q	n
21		直接結合	1		0
22		直接結合	1		0
23		直接結合	1		1
24		直接結合	0		1
25		直接結合	0		1
26		直接結合	1		0
27		直接結合	0		1
28		直接結合	0		1
29		直接結合	0		1
30		直接結合	0		1

【００２３】

【表４】

表－１続きの３

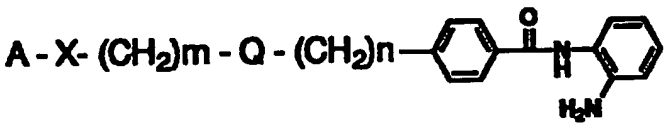


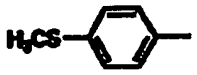
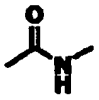
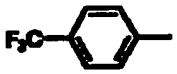
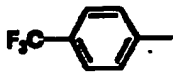
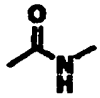
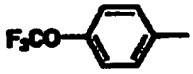
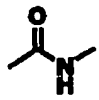
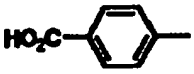
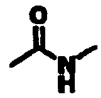
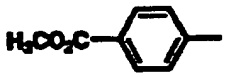
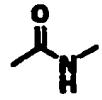
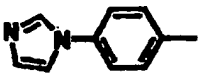
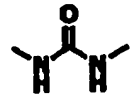
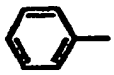
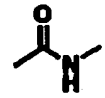
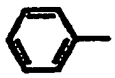
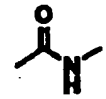
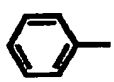
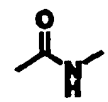
化合物番号	A	X	m	Q	n
３１		直接結合	0		1
３２		直接結合	1		0
３３		直接結合	0		1
３４		直接結合	1		1
３５		直接結合	0		1
３６		直接結合	0		1
３７		直接結合	0		1
３８		直接結合	1		1
３９		直接結合	1		1
４０		直接結合	0		1

【００２４】

【表５】

表－１続きの４

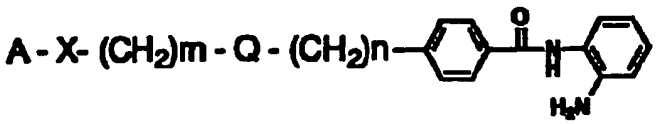


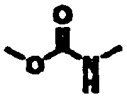
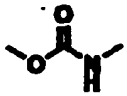
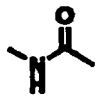
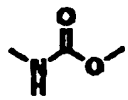
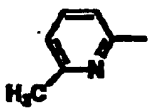
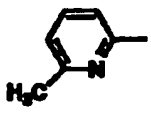
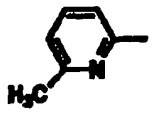
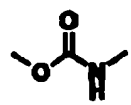
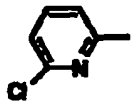
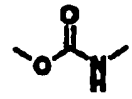
化合物番号	A	X	m	Q	n
４１		直接結合	0		1
４２		直接結合	0		1
４３		直接結合	1		0
４４		直接結合	0		1
４５		直接結合	0		1
４６		直接結合	0		1
４７		直接結合	1		1
４８		—O—	1		1
４９		—S—	1		1
５０		—N—	1		1

【0025】

【表6】

表－1続きの5

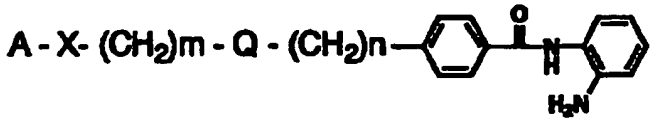


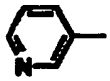
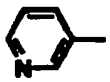
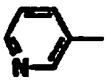
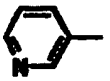
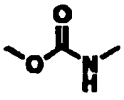
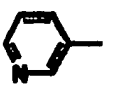
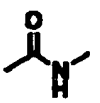
化合物番号	A	X	m	Q	n
51		直接結合	1		1
52		直接結合	2		1
53		直接結合	0		1
54		直接結合	1		0
55		直接結合	1		0
56		直接結合	1		1
57		直接結合	1		0
58		直接結合	0		1
59		直接結合	1		1
60		直接結合	1		1

【0026】

【表7】

表－1続きの6

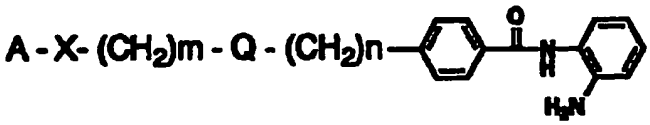


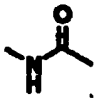
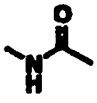
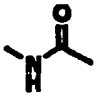
化合物番号	A	X	m	Q	n
61		—O—	1		1
62		—O—	2		1
63		—NH—	1		1
64		—S—	1		1
65		—O—	1		0
66		—O—	2		0
67		—O—	2		0
68		直接結合	1		0
69		直接結合	2		0
70		直接結合	3		0

【0027】

【表8】

表－1続きの7

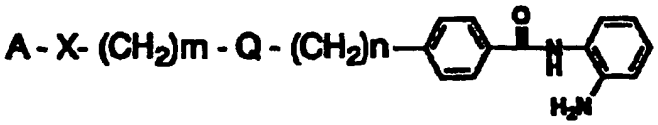


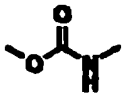
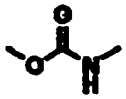
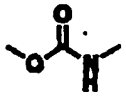
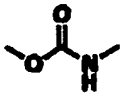
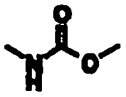
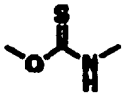
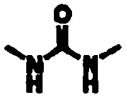
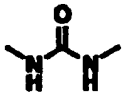
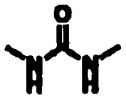
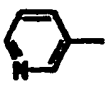
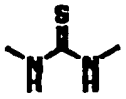
化合物番号	A	X	m	Q	n
71		直接結合	0		1
72		直接結合	0		2
73		直接結合	0		3
74		直接結合	1		1
75		直接結合	2		1
76		直接結合	3		1
77		直接結合	1		2
78		直接結合	1		1
79		直接結合	0		2
80		直接結合	1		2

【0028】

【表9】

表－1続きの8

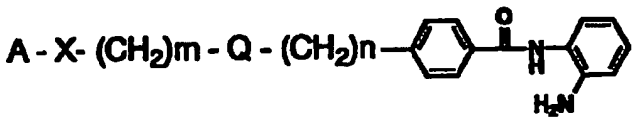


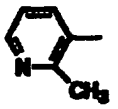
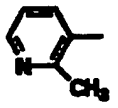
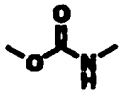
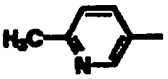
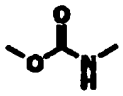
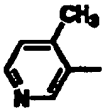
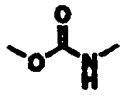
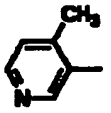
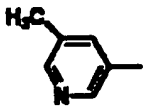
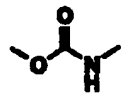
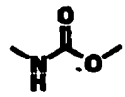
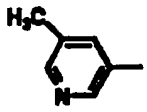
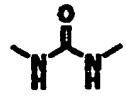
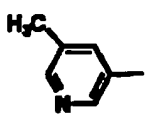
化合物番号	A	X	m	Q	n
81		直接結合	0		1
82		直接結合	1		1
83		直接結合	2		1
84		直接結合	3		1
85		直接結合	1		1
86		直接結合	1		1
87		直接結合	0		1
88		直接結合	1		1
89		直接結合	2		1
90		直接結合	1		1

【0029】

【表10】

表－1続きの9

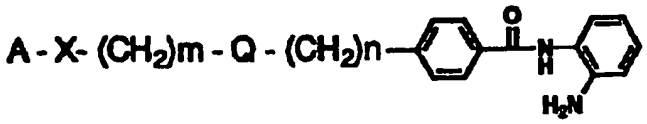


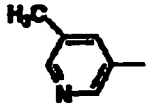
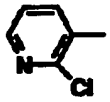
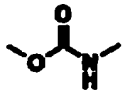
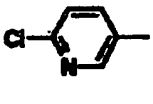
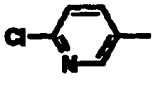
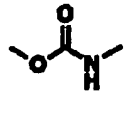
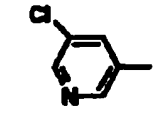
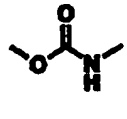
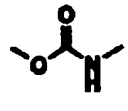
化合物番号	A	X	m	Q	n
91		直接結合	0		1
92		直接結合	1		1
93		直接結合	0		1
94		直接結合	1		1
95		直接結合	1		1
96		直接結合	1		1
97		直接結合	1		1
98		直接結合	1		1
99		直接結合	1		1
100		直接結合	2		1

【００３０】

【表１１】

表－１続きの１０

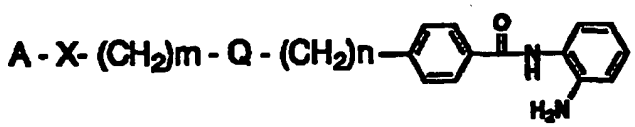


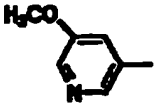
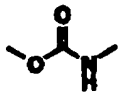
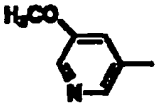
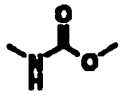
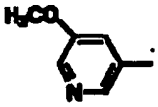
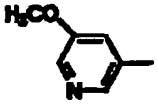
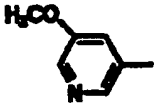
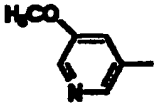
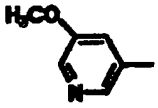
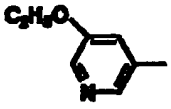
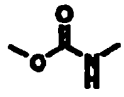
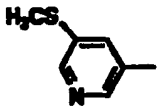
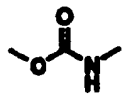
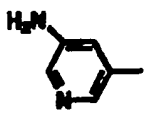
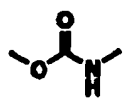
化合物番号	A	X	m	Q	n
１０１		直接結合	2		1
１０２		直接結合	2		0
１０３		直接結合	1		2
１０４		直接結合	0		1
１０５		直接結合	1		1
１０６		直接結合	0		1
１０７		直接結合	1		1
１０８		直接結合	1		1
１０９		直接結合	1		1
１１０		直接結合	1		1

【0031】

【表12】

表－1続きの11

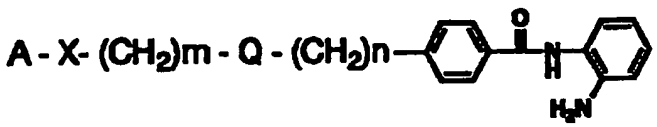


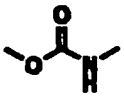
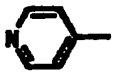
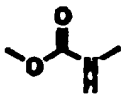
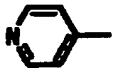
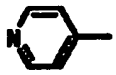
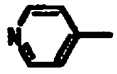
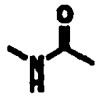
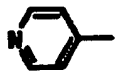
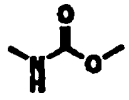
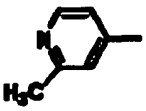
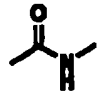
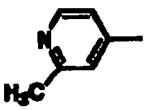
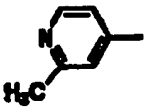
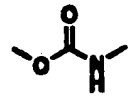
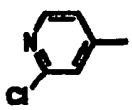
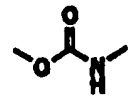
化合物番号	A	X	m	Q	n
111		直接結合	1		1
112		直接結合	1		1
113		直接結合	1		1
114		直接結合	2		1
115		直接結合	2		1
116		直接結合	2		0
117		直接結合	1		2
118		直接結合	1		1
119		直接結合	1		1
120		直接結合	1		1

【００３２】

【表１３】

表－１続きの１２

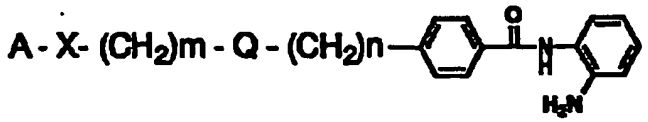


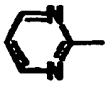
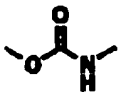
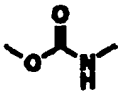
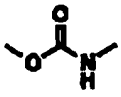
化合物番号	A	X	m	Q	n
１２１		直接結合	1		1
１２２		直接結合	2		1
１２３		直接結合	0		1
１２４		直接結合	1		0
１２５		直接結合	1		0
１２６		直接結合	1		1
１２７		直接結合	1		0
１２８		直接結合	0		1
１２９		直接結合	1		1
１３０		直接結合	1		1

【００３３】

【表１４】

表－１続きの１３

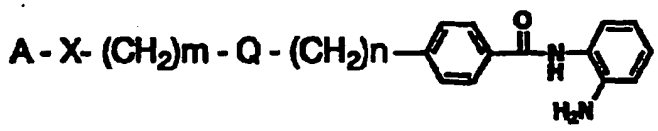


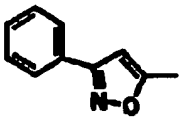
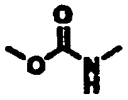
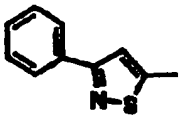
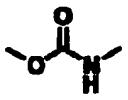
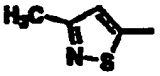
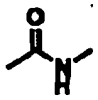
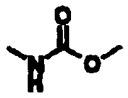
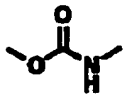
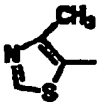
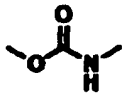
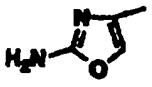
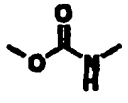
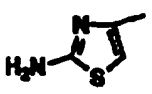
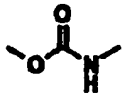
化合物番号	A	X	m	Q	n
１３１		直接結合	0		1
１３２		直接結合	0		1
１３３		直接結合	0		1
１３４		直接結合	0		1
１３５		直接結合	1		1
１３６		直接結合	2		1
１３７		直接結合	0		1
１３８		直接結合	1		1
１３９		直接結合	0		1
１４０		直接結合	0		1

【００３４】

【表１５】

表－１続きの１４

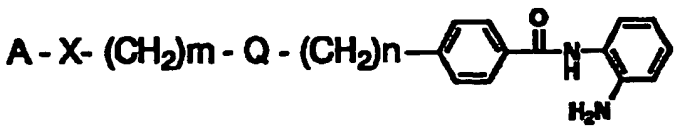


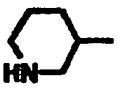
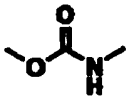
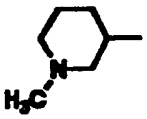
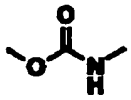
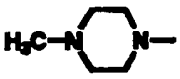
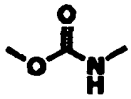
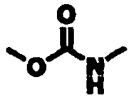
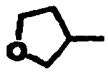
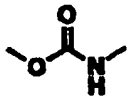
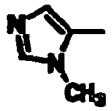
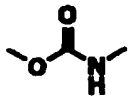
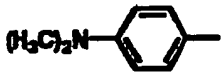
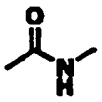
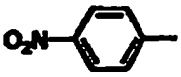
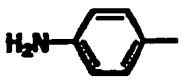
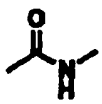
化合物番号	A	X	m	Q	n
１４１		直接結合	1		1
１４２		直接結合	1		1
１４３		直接結合	0		1
１４４		直接結合	0		1
１４５		直接結合	0		1
１４６		直接結合	3		1
１４７		直接結合	1		1
１４８		直接結合	2		1
１４９		直接結合	1		1
１５０		直接結合	1		1

【0035】

【表16】

表－1続きの15



化合物番号	A	X	m	Q	n
151		直接結合	1		1
152		直接結合	1		1
153		直接結合	3		1
154		直接結合	1		1
155		直接結合	1		1
156		直接結合	1		1
157		直接結合	1		0
158		—O—	1		0
159		—O—	1		0

【００３６】

本発明の化合物は、例えば下記のような方法により製造することができる。

（ａ）一般式（４）［化７］

【００３７】

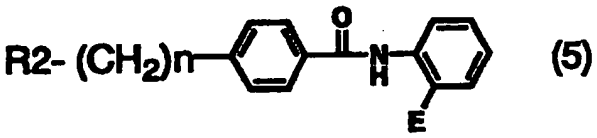
【化７】

$$A\text{-}X\text{-}(CH_2)m\text{-}R1 \qquad (4)$$

［式中、Ａ、Ｘ、ｍは、上記と同義。Ｒ１は、－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）または－NH_2を表す。］で表される化合物と一般式（５）［化８］

【００３８】

【化８】



(5)

［式中、ｎは、上記と同義。Ｒ２は、Ｒ１が－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）のときは－NH_2を表し、Ｒ１が－NH_2のときは－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）を表す。Ｅは、ｔｅｒｔ－ブトキシカルボニル基などの通常のペプチド形成反応に用いられる保護基と結合したアミノ基を表す。］で表される化合物を縮合反応に付すか、

（ｂ）一般式（６）［化９］

【００３９】

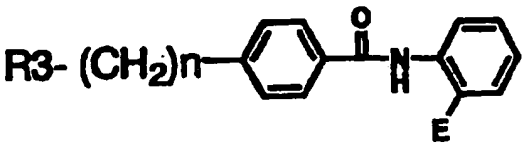
【化９】

$$A\text{-}X\text{-}(CH_2)m\text{-}R3 \qquad (6)$$

（式中、Ａ、Ｘ、ｍは、上記と同義。Ｒ３は、－ＯＨまたは－NH_2を表す。）で表される化合物と一般式（７）［化１０］

【００４０】

【化１０】

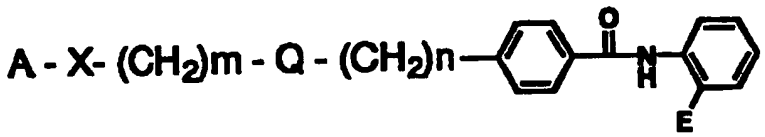


(7)

（式中、Ｒ３、ｎ、Ｅは、上記と同義。）で表される化合物を、Ｎ，Ｎ’－カルボニルジイミダゾール、Ｎ，Ｎ’－チオカルボニルジイミダゾール、ホスゲンまたはチオホスゲンなどを用いて縮合反応に付して得られる一般式（８）［化１１］

【００４１】

【化１１】



(8)

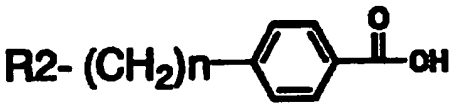
（式中、Ａ、Ｘ、ｍ、Ｑ、ｎ、Ｅは、上記と同義。）で表される化合物のアミノ基の保護基を除去することにより得ることができる。

一般式（４）で表される化合物は市販されているか、後記実施例に記載の方法によって得ることができる。

一般式（５）で示される化合物は、一般式（９）［化１２］

【００４２】

【化１２】

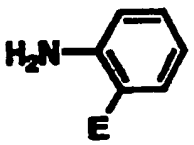


(9)

（式中、Ｒ２、ｎは、上記と同義。）で表される安息香酸誘導体に適当な保護基を導入した後、一般式（１０）［化１３］

【００４３】

【化１３】



(10)

（式中、Eは上記と同義。）で示される化合物と縮合反応に付し、さらに脱保護を行うことにより得ることができる。

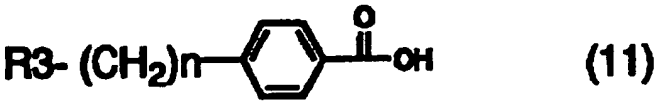
【0044】

一般式（6）で示される化合物は市販されているか、または後記実施例記載の方法によって得ることができる。

一般式（7）で示される化合物は、一般式（11）［化14］

【0045】

【化14】



(11)

（式中、R3、nは上記と同義。）で示される安息香酸誘導体に適当な保護基を導入した後、一般式（10）で示される化合物を縮合反応に付し、さらに脱保護を行うことにより得ることができる。

一般式（11）で示される化合物は市販されているか、または後記実施例記載の方法によって得ることができる。

【0046】

（a）の縮合反応は、通常のペプチドにおけるアミド結合形成反応、例えば活性エステルまたは混合酸無水物または酸塩化物の方法によって実施することができる。例えば、カルボン酸成分［一般式（4）においてR1が－C（＝G）OH（Gは、酸素原子または硫黄原子を表す）で表される化合物または一般式（5）においてR2が－C（＝G）OH（Gは、酸素原子または硫黄原子を表す）で表される化合物］と2、4、5－トリクロロフェノール、ペンタクロロフェノールまたは4－ニトロフェノールなどのフェノール類またはN－ヒドロキシスクシイミド、N－ヒドキシベンズトリアゾールなどのN－ヒドロキシ化合物をジシクロヘキシルカルボジイミドの存在下に縮合させ、活性エステル体に変換した後、アミン成分［一般式（4）においてR1が$-NH_2$で表される化合物または一般式（5）においてR2が$-NH_2$で表される化合物］と縮合させることによって行うことができる。

【００４７】

また、カルボン酸成分［一般式（４）においてＲ１が－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）で表される化合物または一般式（５）においてＲ２が－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）で表される化合物］を塩化オキザリル、塩化チオニル、オキシ塩化リンなどと反応させ、酸塩化物に変換した後、アミン成分［一般式（４）においてＲ１が－NH_2で表される化合物または一般式（５）においてＲ２が－NH_2で表される化合物］と縮合させることによって行うことができる。

【００４８】

また、カルボン酸成分［一般式（４）においてＲ１が－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）で表される化合物または一般式（５）においてＲ２が－Ｃ（＝Ｇ）ＯＨ（Ｇは、酸素原子または硫黄原子を表す）で表される化合物］をクロロ炭酸イソブチルまたはメタンスルホニルクロライドなどと反応させることによって混合酸無水物を得た後、アミン成分［一般式（４）においてＲ１が－NH_2で表される化合物または一般式（５）においてＲ２が－NH_2で表される化合物］と縮合させることによって行うことができる。

さらにまた、当該縮合反応は、ジシクロヘキシルカルボジイミド、Ｎ，Ｎ’－カルボニルジイミダゾール、ジフェニルリン酸アジド、シアノリン酸ジエチルなどのペプチド縮合試薬を単独で用いて行うこともできる。

【００４９】

反応は、通常－２０～＋５０℃で０．５～４８時間行う。用いられる溶媒としては例えば、ベンゼン、トルエンなどの芳香族炭化水素類、テトラヒドロフラン、ジオキサン、ジエチルエーテルなどのエーテル類、塩化メチレン、クロロホルムなどのハロゲン化炭化水素類、Ｎ，Ｎ－ジメチルホルムアミドや、メタノール、エタノールなどのアルコール類またはこれらの混合物が挙げられる。必要により有機塩基例えば、トリエチルアミンまたはピリジンなどを加えて反応する。

【００５０】

（ｂ）の縮合反応は、一般式（６）で表される化合物か一般式（７）で表される化合物のどちらか一方をホスゲン、チオホスゲン、Ｎ，Ｎ’－カルボニルジイ

ミダゾールやN，N'－チオカルボニルジイミダゾールなどを用いて活性化した後、もう一方の化合物と反応させることによって行うことができる。反応は、通常－２０～＋５０℃で０．５～４８時間反応行う。用いられる溶媒としては例えば、ベンゼン、トルエンなどの芳香族炭化水素類、テトラヒドロフラン、ジオキサン、ジエチルエーテルなどのエーテル類、塩化メチレン、クロロホルムなどのハロゲン化炭化水素類、Ｎ，Ｎ－ジメチルホルムアミド、またはこれらの混合物が挙げられる。必要により有機塩基例えば、トリエチルアミンまたはピリジンなどを加えて反応する。

【００５１】

一般式（８）で表される化合物の保護基の除去は、通常のペプチド形成反応に用いられる条件で行われる。例えば、一般式（８）においてＥが、ｔｅｒｔ－ブトキシカルボニル基で保護されたアミノ基の場合は、塩酸などの酸で処理することにより脱保護反応を行うことができる。

【００５２】

一般式（１）で表される化合物の塩は、一般式（１）で表される化合物を製造する反応で得ることもできるが、薬学的に許容される酸と容易に塩を形成しうる。その酸としては、例えば塩酸、臭化水素酸、硫酸、燐酸などの無機酸や、酢酸、酒石酸、フマル酸、マレイン酸、クエン酸、安息香酸、トリフルオロ酢酸、ｐ－トルエンスルホン酸などの有機酸を挙げることができる。これらの塩もまたフリー体の一般式（１）の化合物と同様に本発明の有効成分化合物として用いることができる。

【００５３】

一般式（１）で表される化合物は、反応混合物から通常の分離手段、例えば抽出法、再結晶法、カラムクロマトグラフィーなどの方法により単離精製することができる。

【００５４】

本発明の新規ベンズアミド誘導体は分化誘導作用を有しており、悪性腫瘍、自己免疫疾患、皮膚病などの治療・改善剤として有用である。

ここで悪性腫瘍とは急性白血病、慢性白血病、悪性リンパ腫、多発性骨髄腫、

マクログロブリン血症などの造血器腫瘍や大腸癌、脳腫瘍、頭頸部癌、乳癌、肺癌、食道癌、胃癌、肝癌、胆嚢癌、胆管癌、膵癌、膵島細胞癌、腎細胞癌、副腎皮質癌、膀胱癌、前立腺癌、睾丸腫瘍、卵巣癌、子宮癌、絨毛癌、甲状腺癌、悪性カルチノイド腫瘍、皮膚癌、悪性黒色腫、骨肉腫、軟部組織肉腫、神経芽細胞腫、ウィルムス腫瘍、網膜芽細胞腫などの固形腫瘍が挙げられる。

自己免疫疾患とはリウマチ、腎炎、糖尿病などを示す。

皮膚病とは乾せん、アクネ、湿疹、アトピー性皮膚炎などを示す。

なお、本発明の対象疾患はこれらに限定されることはない。

【００５５】

本発明の有効成分化合物は、医薬品として有用であり、これらは一般的な医療製剤の形態で用いられる。製剤は通常使用される充填剤、増量剤、結合剤、付湿剤、崩壊剤、界面活性剤、滑沢剤等の希釈剤あるいは賦形剤を用いて調製される。この医薬製剤としては各種の形態が治療目的に応じて選択でき、その代表的なものとして錠剤、丸剤、散剤、液剤、懸濁剤、乳剤、顆粒剤、カプセル剤、注射剤（液剤、懸濁剤等）および坐剤等が挙げられる。

【００５６】

錠剤の形態に成形するに際しては、担体としてこの分野で従来よりよく知られている各種のものを広く使用することができる。その例としては、例えば乳糖、白糖、塩化ナトリウム、ブドウ糖、デンプン、炭酸カルシウム、カオリン、結晶セルロース、ケイ酸等の賦形剤、水、エタノール、プロパノール、単シロップ、ブドウ糖液、デンプン液、ゼラチン溶液、カルボキシメチルセルロース、セラック、メチルセルロース、リン酸カリウム、ポリビニルピロリドン等の結合剤、

【００５７】

乾燥デンプン、アルギン酸ナトリウム、カンテン末、炭酸水素ナトリウム、炭酸カルシウム、ポリオキシエチレンソルビタン脂肪酸エステル類、ラウリル硫酸ナトリウム、ステアリン酸モノグリセリド、デンプン、乳糖等の崩壊剤、白糖、ステアリン酸、カカオバター、水素添加油等の崩壊抑制剤、第４級アンモニウム塩基、ラウリル硫酸ナトリウム等の吸収促進剤、グリセリン、デンプン等の保湿剤、デンプン、乳糖、カオリン、ベントナイト、コロイド状ケイ酸等の吸着剤、タ

ルク、ステアリン酸塩、ホウ酸末、ポリエチレングリコール等の滑沢剤等を使用することができる。さらに錠剤については、必要に応じ通常の剤皮を施した錠剤、例えば糖衣錠、ゼラチン被包錠、腸溶性被包錠、フィルムコーティング錠あるいは二層錠、多層錠とすることができる。

【００５８】

丸剤の形態に成形するに際しては、担体として従来この分野で公知のものを広く使用できる。その例としては、例えばブドウ糖、乳糖、デンプン、カカオ脂、硬化植物油、カオリン、タルク等の賦形剤、アラビアゴム末、トラガント末、ゼラチン等の結合剤、カルメロースカルシウム、カンテン等の崩壊剤等が挙げられる。

カプセル剤は、常法に従い通常有効成分化合物を上記で例示した各種の担体と混合して、硬質ゼラチンカプセル、軟質カプセル等に充填して調製される。

【００５９】

注射剤として調製する場合、液剤、乳剤および懸濁剤は殺菌され、かつ血液と等張であることが好ましく、これらの形態に成形するに際しては、希釈剤としてこの分野において慣用されているもの、例えば水、エタノール、マクロゴール、プロピレングリコール、エトキシ化イソステアリルアルコール、ポリオキシ化イソステアリルアルコール、ポリオキシエチレンソルビタン脂肪酸エステル類等を使用することができる。この場合等張性の溶液を調製するのに充分な量の食塩、ブドウ糖あるいはグリセリンを医薬製剤中に含有させてもよく、また通常の溶解補助剤、緩衝剤、無痛化剤等を添加してもよい。

【００６０】

坐剤の形態に成形するに際しては、担体として従来公知のものを広く使用することができる。その例としては、例えばポリエチレングリコール、カカオ脂、高級アルコール、高級アルコールのエステル類、ゼラチン、半合成グリセライド等を挙げることができる。

さらに必要に応じて着色剤、保存剤、香料、風味剤、甘味剤等や他の医薬品を医薬製剤中に含有させることもできる。

本発明のこれらの医薬製剤中に含有されるべき有効成分化合物の量は、特に限

定されずに広範囲から適宜選択されるが、通常製剤組成物中に約１～７０重量％、好ましくは約５～５０重量％とするのがよい。

【００６１】

本発明のこれら医薬製剤の投与方法は特に制限はなく、各種製剤形態、患者の年齢、性別、疾患の程度およびその他の条件に応じた方法で投与される。例えば錠剤、丸剤、液剤、懸濁剤、乳剤、顆粒剤およびカプセル剤の場合には、経口投与され、注射剤の場合は、単独でまたはブドウ糖、アミノ酸等の通常の補液と混合して静脈内投与され、さらに必要に応じて単独で筋肉内、皮下もしくは腹腔内投与される。坐剤の場合は直腸内投与される。

【００６２】

本発明のこれら医薬製剤の投与量は、用法、患者の年齢、性別、疾患の程度およびその他の条件により適宜選択されるが、通常有効成分化合物の量としては、体重１ｋｇ当り、一日約0.0001～100ｍｇ程度とするのがよい。また投与単位形態の製剤中には有効成分化合物が約0.001～1,000ｍｇの範囲で含有されることが望ましい。

本発明の一般式（１）で表される化合物またはその塩は、薬理学的に効果を示す投与量において毒性を示さない。

【００６３】

【実施例】

以下に本発明を実施例で詳細に説明するが、本発明はこれらに限定されるものではない。なお、表題の括弧内の番号は詳細な説明に例示した化合物の番号である。

実施例１

Ｎ－（２－アミノフェニル）－４－（Ｎ－ベンゾイルアミノメチル）ベンズアミド　塩酸塩（表－１：化合物番号１の塩酸塩）の合成

【００６４】

（１－１）　４－アミノメチル安息香酸（２１．１６ｇ，１４０ｍｍｏｌ）のジクロロメタン（４５０ｍｌ）懸濁液に、トリエチルアミン（４２ｍｌ，３００ｍｍｏｌ）を加えた。氷冷下、内温を３～８℃に保ちながら無水トリフルオロ酢酸

（６０．４ｇ，２８７ｍｍｏｌ）のジクロロメタン（５０ｍｌ）溶液を滴下した後、３時間撹拌した。飽和重曹水中に反応液をあけた後、さらに１０％塩酸水溶液で酸性にした。析出したゲル状沈澱物を、濾取、乾燥することにより、４－トリフルオロアセチルアミノメチル安息香酸（３０．４ｇ，収率８７．８％）を乳白色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 4.47(2H,d,5.8), 7.39(2H,d,8.1), 7.93(2H,d,8.1), 10.08(1H,t,5.8), 12.95(1H,br.s).

【００６５】

（１－２）　ｏ－フェニレンジアミン（５４．０ｇ，５００ｍｍｏｌ）のジオキサン（５００ｍｌ）溶液に１規定水酸化ナトリウム水溶液（２５０ｍｌ）を加え、氷冷下ジｔｅｒｔ－ブトキシジカーボネート（１０９．１ｇ，５５０ｍｍｏｌ）のジオキサン（２５０ｍｌ）溶液を加えた。室温で６時間撹拌後、一晩放置した。溶媒を１／２容にまで濃縮した後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得た残渣をシリカゲルカラムクロマトグラフィー（クロロホルム）で精製し、得られた固体をエチルエーテルで洗浄することによりＮ－ｔｅｒｔ－ブトキシカルボニル－ｏ－フェニレンジアミン（３４．２ｇ，収率３２．８％）を白色固体として得た。

1H NMR(270MHz, CDCl3) δ ppm: 1.51(9H,s), 3.75(2H,s), 6.26(1H,s), 6.77(1H,d,J=8.1Hz), 6.79(1H,dd,J=7.3,8.1Hz), 7.00(1H,dd,J=7.3,8.1Hz), 7.27(1H,d,J=8.1Hz).

【００６６】

（１－３）　工程（１－１）で得られた化合物（３０．０ｇ，１２１ｍｍｏｌ）のジクロロメタン（２００ｍｌ）懸濁液に、氷冷しながら（内温１０～１５℃）オキザリルクロライド（２１ｇ，１６５ｍｍｏｌ）を徐々に滴下した。その際にときどき（およそ２ｍｌ滴下する毎に０．１ｍｌ）ＤＭＦを加えた。全量滴下後、発泡が止まるまで撹拌し、その後４０℃で１時間撹拌した。溶媒を留去した後、トルエンで過剰のオキザリルクロライドを共沸し、再度ジクロロメタン（１００ｍｌ）に溶解した。工程（１－２）で得られた化合物（２２．８８ｇ，１１０ｍｍｏｌ）のジクロロメタン（１００ｍｌ）－ピリジン（２００ｍｌ）溶液に、

先に調製した酸クロライド溶液を氷冷下（内温７～９℃）滴下した。

【００６７】

滴下終了後、室温まで昇温させた後、一晩放置した。反応混合物に飽和重曹水を加えた後、クロロホルムで抽出し、飽和食塩水で洗浄後、乾燥、溶媒を留去した。得られた残渣にメタノールージイソプロピルエーテルを加え、析出した固体を濾取、乾燥することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－トリフルオロアセチルアミノメチルベンズアミド（２８．１ｇ；収率５８％）を淡黄色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.44(9H,s), 4.48(2H,d,5.9), 7.12-7.23(2H,m), 7.44(2H,d,8.1), 7.54(2H,d,8.1), 7.94(2H,d,8.1), 8.68(1H,br.s), 9.83(1H,s), 10.10(1H,br.t,5.9).

【００６８】

（１－４） 工程（１－３）の化合物（１３．１２ｇ，３０ｍｍｏｌ）のメタノール（１２０ｍｌ）－水（１８０ｍｌ）懸濁液に炭酸カリウム（４．７０ｇ，３４．０ｍｍｏｌ）を加え、７０℃で４時間加熱撹拌した。クロロホルムで抽出し、有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去し、乾燥することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－アミノメチルベンズアミド（１０．３ｇ；定量的）を淡黄色アモルファス状固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 3.80(2H,s), 7.13-7.23(2H,m), 7.48-7.58(4H,m), 7.90(2H,d,8.1), 8.69(1H,br.s), 9.77(1H,br.s).

【００６９】

（１－５） 工程（１－４）の化合物（０．１１ｇ，０．４４ｍｍｏｌ）のピリジン（５ｍｌ）溶液に氷冷下、ベンゾイルクロライド（０．０８ｇ，０．５３ｍｍｏｌ）を加えた後、室温まで徐々に温度を上げながら８時間撹拌した。飽和重曹水を加えた後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、乾燥、溶媒を留去して得られた残渣をジイソプロピルエーテルで洗浄し、得られた固体を乾燥することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－（Ｎ－ベンゾイルアミノメチル）ベンズアミド（０．１４ｇ

，７１．４％）を白色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.44(9H,s), 4.56(2H,d,5.9), 7.11-7.22(2H,m), 7.46-7.56(7H,m), 7.90-7.94(4H,m), 8.67(1H,s), 9.15(1H,t, 5.9), 9.81(1H,s)

【００７０】

（１－６）　工程（１－５）の化合物（０．１０ｇ，０．２２４ｍｍｏｌ）のジオキサン（５ｍｌ）－メタノール（１ｍｌ）溶液に４規定塩酸－ジオキサン（５ｍｌ）を加え、室温で７時間撹拌した。溶媒を留去した残渣にジイソプロピルエーテルを加え、得られた固体を濾取、乾燥することにより、Ｎ－（２－アミノフェニル）－４－（Ｎ－ベンゾイルアミノメチル）ベンズアミド塩酸塩（０．０８ｇ，９３％）を淡褐色固体として得た。

mp. 206-209℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.57(2H,d,5.8), 7.27-7.38(4H,m), 7.47-7.59(5H,m), 7.92(1H,d,8.1), 8.05(1H,d,8.1), 9.19(1H,t,5.8), 10.38(1H,br.s)

IR(KBr,cm-1): 3286,3003(br.),1630,1551,1492,1306,1250,749,695.

実施例１に記載と同様の方法により、実施例２から実施例３０の化合物を合成した。以下に、化合物の融点（mp.）、1H NMR、IRの測定値を示す。

【００７１】

実施例２

Ｎ－（２－アミノフェニル）－４－［Ｎ－（２－クロロベンゾイル）アミノメチル］ベンズアミド（表－１：化合物番号１４）

mp. 201-204℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.52(2H,t,5.9), 4.89(2H,br.s), 6.60(1H,ddd,1.5,7.3,8.1), 6.78(1H,dd,1.5,8.1), 6.97(1H,ddd,1.5,7.3,8.1), 7.17(1H,d,8.1), 7.38-7.54(6H,m), 7.97(2H,d,8.1), 9.06(1H,br.t,5.9), 9.63(1H,br.s).

IR(KBr)cm-1: 3268,1649,1458,1304,748.

【００７２】

実施例３

Ｎ－（２－アミノフェニル）－４－［Ｎ－（２－ニトロベンゾイル）アミノメチ

ル] ベンズアミド塩酸塩（表－１：化合物番号１８の塩酸塩）

mp. 210-212℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.55(2H,t,5.9), 7.2-7.4(3H,m), 7.5-7.6(1H, m), 7.53(2H,d,8.1), 7.60-7.7(2H,m), 7.83(1H,ddd,1.5,8.1,8.1), 8.00-8.10(3H,m), 9.34(1H,t,5.9), 10.43(1H,br.s).

IR(KBr)cm-1: 3283,2500-3000(br.),1648,1534,1461,1362,1314,754,701.

【００７３】

実施例４

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－メチルベンゾイル）アミノメチル］ベンズアミド塩酸塩（表－１：化合物番号２８の塩酸塩）

mp. (amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 2.37(3H,s), 4.56(2H,d,5), 7.20-7.30(6H,m), 7.47(4H,d,8.8), 7.82(2H,d,8.8), 8.03(2H,d,8.8), 9.09(1H,t,5), 10.36(1H, br.s).

IR(KBr)cm-1: 3269(br.),2861(br.),1743,1636,1534,1505,1456,1308,1120,753.

【００７４】

実施例５

Ｎ－（２－アミノフェニル）－４－［Ｎ－（３－メトキシベンゾイル）アミノメチル］ベンズアミド（表－１：化合物番号３０）

mp. 182-185℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.81(3H,s), 4.54(2H,d,5.9), 4.88(2H,br.s), 6.60(1H,dd,6.6,7.3), 6,78(1H,d,7.3), 6.97(1H,dd,6.6,7.3), 7.11(1H,dd,1.5,8.1), 7.16(1H,d,7.3), 7.35-7.51(5H,m), 7.94(2H,d,8.1), 9.12(1H,br.t,5.9), 9.63(1H,br.s).

IR(KBr)cm-1: 3301,1637,1524,1489,1457,1314,1248,752.

【００７５】

実施例６

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－メトキシベンゾイル）アミノメチル］ベンズアミド（表－１：化合物番号３１）

mp. 149-151℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.82(3H,s), 4.53(2H,d,5.9), 4.88(2H,s), 6.59(1H,dd,7.3,7.3), 6.77(1H,d,8.1), 6.94-7.0(1H,m), 7.02(2H,d,8.8), 7.16(1H,d,8.1), 7.43(2H,d,8.1), 7.89(2H,d,8.8), 7.94(2H,d,8.1), 8.98(1H,br.t, 5.9), 9.61(1H,br.s)

IR(KBr)cm-1: 3297,1630,1527,1505,1457,1256,1177,1024,843,749.

【００７６】

実施例７

Ｎ－（２－アミノフェニル）－４－［Ｎ－（３，４，５－トリメトキシベンゾイル）アミノメチル］ベンズアミド（表－１：化合物番号３３）

mp. 208-210℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 3.71(3H,s), 3.83(6H,s), 4.55(2H,d,5.9), 4.88(2H,br.s), 6.60(1H,dd,7.3,8.1), 6.78(1H,d,8.1), 6.97(1H,dd,6.6,8.1), 7,16(1H,d,8.1), 7.26(2H,s), 7.44(2H,d,8.1), 7.95(2H,d,8.8), 9.07(1H,t,5.9), 9.62(1H,br.s).

IR(KBr)cm-1: 3267,1635,1582,1457,1237,1132,755.

【００７７】

実施例８

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－（Ｎ，Ｎ－ジメチル）アミノベンゾイル）アミノメチル］ベンズアミド（表－１：化合物番号３６）

mp. 216-219℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 2.98(6H,s), 4.51(2H,d,5.9), 4.88(2H,br.s), 6.60(1H,dd,8.1,8.1), 6.71(2H,d,8.8), 6.97(1H,ddd,7.3,8.1), 7.16(1H,d,7.3), 7.41(2H,d,8.1), 7.78(2H,d,8.8), 7.93(2H,d,8.1), 8.77(1H,t,5.9), 9.63(1H,br.s).

IR(KBr)cm-1: 3301,1632,1519,1457,1298,754.

【００７８】

実施例９

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－トリフルオロメチルベンゾイル

) アミノメチル] ベンズアミド（表－１：化合物番号４２の化合物）

mp. 243-246℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H,d,5.9), 4.88(2H,br.s), 6.59(1H,dd, 6.6,7.3), 6.77(1H,d,8.1), 6.94(1H,dd,5.9,6.6), 7.16(1H,d,8.1), 7.45(2H,d ,8.1), 7.88(2H,d,8.8), 7.95(2H,d,8.1), 8.11(2H,d,8.1), 9.38(1H,t,5.9), 9 .64(1H,br.s).

IR(KBr)cm-1: 3301,1640,1549,1523,1458,1334,1162,1120,1070,856,750.

【００７９】

実施例１０

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－カルボキシベンゾイル）アミノメチル］ベンズアミド塩酸塩（表－１：化合物番号４５の塩酸塩）

mp. (amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H,d,5.9), 7.29-7.37(3H,m), 7.49(3H,d ,8.1), 8.02-8.06(6H,m), 9.36(1H,t,5.9), 10.4(1H,br.s).

IR(KBr)cm-1: 3432(br.),1718,1637,1542,1499,1303(br.),1116,1018,757.

【００８０】

実施例１１

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－メトキシカルボニルベンゾイル）アミノメチル］ベンズアミド（表－１：化合物番号４６）

mp. 204-209(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 3.89(3H,s), 4.57(2H,d,5.9), 4.88(2H,br.s), 6.60(1H,dd,6.6,7.3), 6.78(2H,d,7.3), 6.97(1H,ddd,1.5,6.6,7.3), 7.16(1H, d,7.3), 7.45(2H,d,8.1), 7.95(2H,d,8.1), 8.03(2H,d,8.8), 8.07(2H,d,8.8), 9.35(1H,t,5.9), 9.64(1H,br.s).

IR(KBr)cm-1: 3287(br.),1721,1634,1281,1113,750,703.

【００８１】

実施例１２

Ｎ－（２－アミノフェニル）－４－（Ｎ－ピコリノイルアミノメチル）ベンズアミド（表－１：化合物番号５３）

mp. 173-178(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.57(2H,d,6.6), 4.88(2H,br.s), 6.59(1H,dd, 7.3,8.1), 6.77(1H,d,8.1), 6.96(1H,dd,7.3,8.1), 7.16(1H,d,7.3), 7.44(2H,d ,8.1), 7.60-7.65(1H,m), 7.93(2H,d,8.1), 7.98-8.08(2H,m), 8.67(1H,d,4.4), 9.45(1H,t,6.6), 9.61(1H,br.s).

IR(KBr)cm-1: 3330,1656,1634,1523,1456,1294,752.

【００８２】

実施例１３

Ｎ－（２－アミノフェニル）－４－［Ｎ－（６－メチルピコリノイル）アミノメチル］ベンズアミド（表－１：化合物番号５８）

mp. 172-173℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.51(3H,s), 4.57(2H,d,6.6), 5.0(2H,br.s), 6.61(1H,dd,7.3,8.1), 6.79(1H,d,7.3), 6.98(1H,dd,7.3,8.1), 7.17(1H,d,7.3) , 7.44(2H,d,8.1), 7.43-7.49(1H,m), 7.84-7.90(2H,m), 7.94(2H,d,8.1), 9.27 (1H,t,5.9), 9.64(1H,br.s).

IR(KBr)cm-1: 3331,1675,1634,1594,1523,1454,1307,1292,750.

【００８３】

実施例１４

Ｎ－（２－アミノフェニル）－４－（Ｎ－ニコチノイルアミノメチル）ベンズアミド（表－１：化合物番号７１）

mp. 193-196℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H,d), 4.88(2H,br.s), 6.60(1H,t), 6.78(1H,d), 6.97(1H,t), 7.16(1H,d), 7.46(2H,d), 7.53(1H,dd), 7.95(2H,d), 8.24(1H,ddd), 8.73(1H,dd), 9.07(1H,d), 9.32(1H,br.t), 9.63(1H,br.s)

IR(KBr,cm-1): 3301,1639,1522,1457,1314,749,705.

【００８４】

実施例１５

Ｎ－（２－アミノフェニル）－４－［Ｎ－（２－メチルニコチノイル）アミノメチル］ベンズアミド（表－１：化合物番号９１）

mp. 191-194℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 2.53(3H,s), 4.53(2H,d,5.9), 4.88(2H,br.s), 6.60(1H,dd,6.6,8.1), 6.78(1H,d,7.3), 6.97(1H,dd,7.3,8.1), 7.17(1H,d,7.3), 7.29(1H,dd,5.1,8.1), 7.47(2H,d,8.1), 7.77(1H,dd,1.5,8.1), 7.97(2H,d,8.1), 8.51(1H,dd,1.5,5.1), 9.06(1H,t,5.9), 9.64(1H,s).

IR(KBr)cm-1: 3261,1642,1523,1310,753.

【００８５】

実施例１６

Ｎ－（２－アミノフェニル）－４－［Ｎ－（６－メチルニコチノイル）アミノメチル］ベンズアミド（表－１：化合物番号９３）

mp. 186-190℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 2.36(3H,s), 4.56(2H,d,5.9), 4.88(2H,s), 6.60(1H,dd,7.4,7.8), 6.78(1H,d,7.8), 6.97(1H,dd,6.9,6.9), 7.16(1H,d,7.4), 7.37(1H,d,8.3), 7.45(2H,d,8.3), 7.95(2H,d,8.3), 8.13(1H,dd,2.0,8.3), 8.96(1H,s), 9.24(1H,t,5.9), 9.63(1H,br.s).

IR(KBr)cm-1: 3302,1636,1602,1523,1489,1457,1313,751.

【００８６】

実施例１７

Ｎ－（２－アミノフェニル）－４－［Ｎ－（２－クロロニコチノイル）アミノメチル］ベンズアミド（表－１：化合物番号１０５）

mp. 176-178℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.54(2H,t,5.9), 4.90(2H,br.s), 6.60(1H,ddd,1.5,7.3,7.3), 6.78(1H,d,8.1), 6.97(1H,ddd,1.5,7.3,7.3), 7.18(1H,d,8.1), 7.48-7.54(3H,m), 7.94-7.99(3H,m), 8.49(1H,dd,2.1,5.1), 9.23(1H,br.t,5.9), 9.65(1H,br.s).

IR(KBr)cm-1: 3264,1649,1524,1400,1309,751.

【００８７】

実施例１８

Ｎ－（２－アミノフェニル）－４－［Ｎ－（６－クロロニコチノイル）アミノメ

チル] ベンズアミド（表－１：化合物番号１０７）

mp. 205-208℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 5.57(2H,d,5.9), 6.60(1H,dd,7.3,7.3), 6.78(1H,d,8.1), 6.96(1H,dd,7.3,8.1), 7.16(1H,d,8.1), 7.45(2H,d,8.1), 7.66(1H,d,8.8), 7.95(2H,d,8.1), 8.27-32(1H,m), 8.90(1H,d,2.1), 9.38(1H,t,5.9), 9.63(1H,s).

IR(KBr)cm-1: 3318(br.),2929,1646,1590,1525,1503,1454,1108,745.

【００８８】

実施例１９

Ｎ－（２－アミノフェニル）－４－（Ｎ－イソニコチノイルアミノメチル）ベンズアミド（表－１：化合物番号１２３）

mp. 234-237℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.57(2H,t,5.9), 4.88(2H,br.s), 6.59(1H,dd,6.6,7.3), 6.78(1H,d,8.1), 6.96(1H,dd,7.3,7.3), 7.16(1H,d,7.3), 7.45(2H,d,8.1), 7.81(2H,d,1.5,4.4), 7.95(2H,d,8.1), 8.75(2H,d,6.6), 9.41(1H,t,5.9), 9.62(1H,br.s).

IR(KBr)cm-1: 3298,1646,1550,1525,1457,1304,843,760,695.

【００８９】

実施例２０

Ｎ－（２－アミノフェニル）－４－［Ｎ－（ピラジン－２－イル）カルボニルアミノメチル］ベンズアミド（表－１：化合物番号１３１）

mp. 207℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H,d,5.9), 4.88(2H,br.s), 6.59(1H,dd,7.3,7.3), 6.77(1H,d,8.1), 6.94(1H,ddd,1.5,7.3,8.1), 7.15(1H,d,7.3), 7.45(2H,d,8.1), 7.93(2H,d,8.1), 8.77(1H,d,1.5), 8.90(1H,d,2.1), 9.21(1H,s), 9.55-9.61(2H,m).

IR(KBr)cm-1: 3368(br.),1657,1524,1455,1295,1023,751.

【００９０】

実施例２１

N－（2－アミノフェニル）－4－［N－（チオフェン－2－イル）カルボニルアミノメチル］ベンズアミド（表－1：化合物番号134）

mp. 202-205℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.52(2H,t,5.9), 4.88(2H,br.s), 6.60(1H,dd, 6.6,7.3), 6.78(1H,d,8.1), 6.97(1H,dd,7.3,8.1), 7.15-7.18(2H,m), 7.43(2H, d,8.1), 7.78(1H,d,4.4), 7.82(1H,d,3.7), 7.95(2H,d,8.1), 9.12(1H,br.t,5.9), 9.62(1H,br.s).

IR(KBr)cm-1: 3306,1633,1523,1456,1297,750,716.

【0091】

実施例22

N－（2－アミノフェニル）－4－（N－フロイルアミノメチル）ベンズアミド

（表－1：化合物番号137）

mp. 197℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.59(2H,d,6.6), 4.86(2H,br.s), 6.59(1H,t,6.6), 6.63(1H,dd,1.5,3.6), 6.78(1H,d,8.1), 6.96(1H,dd,7.3,6.6), 7.10-7.20(2H,m), 7.41(2H,d,8.1), 7.84(1H,s), 7.94(2H,d,8.1), 9.00(1H,br.t, 5.9), 9.62(1H,s).

IR(KBr)cm-1: 3245,1651,1573,1545,1323,1241,745.

【0092】

実施例23

N－（2－アミノフェニル）－4－［N－（ピロール－2－イル）カルボニルアミノメチル］ベンズアミド（表－1：化合物番号139）

mp. 216-220℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 4.50(2H,d,5.9), 4.88(2H,br.s), 6.10(1H,dd,2.1,5.9), 6.59(1H,dd,7.3,7.3), 6.77(1H,dd,1.5,8.1), 6.84-6.88(2H,m), 6.97(1H,ddd,1.5,7.3,8.1), 7.16(1H,d,7.3), 7.41(2H,d,8.1), 7.94(2H,d,8.1), 8.62(1H,br.t,5.9), 9.62(1H,br.s).

IR(KBr)cm-1: 3275,1655,1584,1534,1458,1316,747.

【0093】

実施例24

N－（2－アミノフェニル）－4－［N－（N'－メチルピロール－2－イル）カルボニルアミノメチル］ベンズアミド（表－1：化合物番号140）

mp. 177-179℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 3.84(3H,s), 4.46(2H,d,5.9), 4.88(2H,d,5.9), 6.03(1H,dd,2.1,4.4), 6.59(1H,dd,8.1,8.1), 6.77(1H,d,8.1), 6.84-6.97(2H,m), 7.16(1H,d,7.3), 7.41(2H,d,8.1), 7.93(2H,d,8.1), 8.61(1H,t,5.9), 9.62(1H,br.s).

IR(KBr)cm-1: 3325(br.),1630,1551,1520,1507,1324,1265,1154,740.

【0094】

実施例２５

Ｎ－（２－アミノフェニル）－４－［Ｎ－（イソオキサゾール－５－カルボニル）アミノメチル］ベンズアミド（表－１：化合物番号１４３）

mp. 183-185℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.53(2H,d,6.6), 4.89(2H,br.s), 6.60(1H,dd,7.3,7.3), 6.78(1H,d,7.3), 6.97(1H,dd,7.3,8.1), 7.12(1H,d,2.1), 7.16(1H,d,8.1), 7.44(2H,d,8.1), 7.95(2H,d,8.1), 8.76(1H,d,1.5), 9.61(1H,t,5.9), 9.64(1H,br.s).

IR(KBr)cm-1: 3278(br.),1636,1576,1522,1458,1220,749.

【００９５】

実施例２６

Ｎ－（２－アミノフェニル）－４－［Ｎ－（３－メチルイソチアゾール－５－カルボニル）アミノメチル］ベンズアミド（表－１：化合物番号１４４）

mp. 168-169℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.47(3H,s), 4.54(2H,d,5.9), 4.89(2H,br.s), 6.60(1H,dd,7.3,7.3), 6.78(1H,d,7.3), 6.97(1H,ddd,1.0,7.3,8.1), 7.17(1H,d,7.3), 7.44(2H,d,8.1), 7.73(1H,s), 7.96(2H,d,8.1), 9.44(1H,t,5.9), 9.64(1H,br.s).

IR(KBr)cm-1: 3310,1637,1503,1294,751.

【００９６】

実施例２７

Ｎ－（２－アミノフェニル）－４－［Ｎ－（イミダゾール－４－カルボニル）アミノメチル］ベンズアミド（表－１：化合物番号１４５）

mp.(amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.49(2H,d,6.4), 4.87(2H,br.s), 6.59(1H,dd,6.9,6.9), 6.77(1H,d,6.9), 6.96(1H,dd,7.4,7.4), 7.16(1H,d,6.9), 7.41(2H,d,6.9),7.64(1H,br.s), 7.73(1H,br.s), 7.92(2H,d,6.9), 8.56(1H,br.t,6.4), 9.61(1H,s), 12.5(1H,br.s).

IR(KBr)cm-1: 3278(br.),1636,1576,1522,1458,1220,749.

【００９７】

実施例２８

Ｎ－（２－アミノフェニル）－４－［Ｎ－（３－アミノフェニル）アセチルアミノメチル］ベンズアミド（表－１：化合物番号２３の化合物）

mp. 171-176℃

1H NMR(270MHz, DMSO-d6) δ ppm: 4.34(2H,d,J=5.9Hz), 5.24(4H,br.s), 6.48-6.63(4H,m), 6.78-6.81(1H,m), 6.94-7.00(2H,m), 7.18(1H,d,J=8.1Hz), 7.34(2H,d,J=8.1Hz), 7.92(2H,d,J=8.1Hz), 8.50(1H,t,J=5.9Hz), 9.61(1H,s).

【００９８】

実施例２９

Ｎ－（２－アミノフェニル）－４－［Ｎ－（ピリジン－３－イル）アセチルアミノメチル］ベンズアミド（表－１：化合物番号７４）

mp. 127℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.84(2H,s),4.40(2H,d,J=5.88),7.15-7.29(3H,m),7.37(1H,d,J=6.62),7.43(2H,d,J=8.80),7.96(1H,m),7.98(2H,d,J=8.80),8.40(1H,d,J=8.80),8.79-8.87(3H,m),10.20(1H,s).

【００９９】

実施例３０

Ｎ－（２－アミノフェニル）－４－［３－（ピリジン－３－イル）プロピオンアミド］メチルベンズアミド（表－１：化合物番号７５の化合物）

mp. 183-186℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.51(2H,t,7.3), 2.88(2H,d,7.3), 4.31(2H,d,5.9), 4.89(2H,br.s), 6.60(1H,dd,7.3,8.1), 6.78(1H,d,8.1), 6.97(1H,ddd,1.5,7.3,8.1), 7.16(1H,d,8.1), 7.23(2H,d,8.8), 7.28-7.33(1H,m), 7.63(1H,d,8.1), 7.89(2H,d,8.1), 8.41-8.45(3H,m), 9.62(1H,br.s).

IR(KBr)cm-1: 3407,3313,1640,1552,1522,1456,1309,746,717.

【０１００】

実施例３１

Ｎ－（２－アミノフェニル）－４－［Ｎ－（ピリジン－３－イル）オキシアセチ

ルアミノメチル］ベンズアミド（表－１：化合物番号６１の化合物）の合成

（３１－１） 水素化ナトリウム０．２２ｇ（５．５ｍｍｏｌ）のＤＭＦ（２ｍｌ）懸濁液に、３－ヒドロキシピリジン０．４８ｇ（５．０ｍｍｏｌ）のＤＭＦ（２ｍｌ）溶液を室温で滴下した後、１時間攪拌した。得られた褐色溶液を氷冷した後、ブロモ酢酸 ｔｅｒｔ－ブチルエステル０．８１ｍｌ（５．５ｍｍｏｌ）を加え、氷冷下で１時間、室温で２時間攪拌した。水を加えた後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム：酢酸エチル＝５：１）で精製することにより、３－ピリジルオキシ酢酸 ｔｅｒｔ－ブチルエステル０．３４ｇ（収率３２．５％）を無色油状物として得た。

1H NMR(CDCl3) δ ppm: 1.49(9H,s), 4.56(2H,s), 7.18-7.24(2H,m), 8.26(1H,dd, J=1.5,3.6Hz), 8.32(1H,d,J=2.9).

【０１０１】

（３１－２） 工程（３１－１）の化合物０．１４ｇ（０．６７ｍｍｏｌ）のジクロロメタン（２ｍｌ）溶液にトリフルオロ酢酸２ｍｌを加えて室温で３時間攪拌した。溶媒を留去した後、ジイソプロピルエーテルを加え、析出した固体を濾取、乾燥することにより、３－ピリジルオキシ酢酸トリフルオロ酢酸塩０．１５ｇ（収率８３．８％）を淡黄色固体として得た。

1H NMR(DMSO-d6) δ ppm: 4.86(2H,s), 7.57(1H,dd,J=4.4,8.1Hz), 7.67(1H,ddd,J=1.5,1.5,8.8Hz), 8.31(1H,d,J=5.1Hz), 8.46(1H,d,J=2.1Hz), 13(1H,br.s).

【０１０２】

（３１－３） 工程（３１－２）の化合物１００ｍｇ（０．３７ｍｍｏｌ）および実施例１の工程（１－４）で得られた化合物２５５ｍｇ（０．７５ｍｍｏｌ）のジクロロメタン（５ｍｌ）懸濁液にトリエチルアミン０．１４ｍｌ（１．０ｍｍｏｌ）を加え、氷冷した。氷冷下２－クロロ－Ｎ，Ｎ’－ジメチルイミダゾリニイウムクロライド１４０ｍｇ（０．８３ｍｍｏｌ）のジクロロメタン（６ｍｌ）溶液を加え、室温まで昇温させながら７時間攪拌した後、室温で一晩放置した。水および飽和食塩水を加えた後、クロロホルムで抽出した。

【０１０３】

有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル：メタノール＝１０：１）で精製することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－［Ｎ－（ピリジン－３－イル）オキシアセチルアミノメチル］ベンズアミド０．３７ｇ（定量的）を無色油状物として得た。

1H NMR(CDCl3) δ ppm: 1.52(9H,s), 4.62(2H,s), 4.63(2H,d,J=7.3Hz), 6.76(1H, br.s), 6.9-7.0(1H,br.s), 7.15-7.35(5H,m), 7.40(2H,d,J=8.1Hz), 7.82(1H,d, J=8.1Hz), 7.95(2H,d,J=8.1Hz), 8.32(1H,dd,J=2.1,4.4Hz), 8.37(1H,d,J=2.8Hz), 9.20(1H,br.s).

【０１０４】

（３１－４）　工程（３１－３）の化合物１７５ｍｇ（０．３７ｍｍｏｌ）のジオキサン（２ｍｌ）－メタノール（２ｍｌ）溶液に、４規定塩酸－ジオキサン（２ｍｌ）を加えて室温で２時間撹拌した。飽和重曹水を加えた後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣にメタノールおよびジイソプロピルエーテルを加え、析出した固体を濾取、乾燥することにより、Ｎ－（２－アミノフェニル）－４－［Ｎ－（ピリジル－３－イル）オキシアセチルアミノメチル］ベンズアミド９０ｍｇ（収率６４．６％）を乳白色固体として得た。

1H NMR(DMSO-d6) δ ppm: 4.42(2H,d,J=5.9Hz), 4.69(2H,s), 4.89(2H,br.s), 6.5 9(1H,dd,J=7.3,8.1Hz), 6.78(1H,d,J=8.1Hz), 6.97(1H,dd,J=6.6,7.3Hz), 7.16(1H,d,J=7.3Hz), 7.33-7.39(4H,m), 7.92(2H,d,J=8.1Hz), 8.21(1H,dd,J=1.5,4.4 Hz), 8.35(1H,d,J=2.9Hz), 8.80(1H,br.t,J=5.9Hz), 9.63(1H,br.s).

IR(KBr)cm-1: 3307, 1672, 1631, 1523, 1456, 1429, 1269, 1231, 803, 1756.

【０１０５】

実施例３２

Ｎ－（２－アミノフェニル）－４－［（ピリジン－３－イル）メトキシカルボニル］アミノメチルベンズアミド（表－１：化合物番号８２の化合物）の合成

（３２－１）　３－ピリジルメタノール３８４ｍｇ（３．５２ｍｍｏｌ）を５ｍｌの乾燥ＴＨＦに溶解し、Ｎ，Ｎ’－カルボニルジイミダゾール５２３ｍｇ（３

．２２ｍｍｏｌ）を室温で加えた。１時間撹拌した後、実施例１の工程（１－４）の化合物１．０ｇ（２．９３ｍｍｏｌ）の乾燥ＴＨＦ溶液６ｍｌを加えた。

【０１０６】

室温で一夜放置後、クロロホルム１００ｍｌを加え、水２０ｍｌで３回洗浄した。ついで飽和食塩水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去後、シリカゲルカラムクロマトグラフィー（クロロホルム：メタノール＝３０：１）で精製し、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－［（ピリジン－３－イル）メトキシカルボニル］アミノメチルベンズアミド１．２７ｇをアモルファス状固体として得た（定量的）。

1H NMR(270MHz, CDCl3) δ ppm: 1.51(9H,s), 4.45(2H,d,J=5.9Hz), 5.16(1H,s), 7.1-7.5(7H,m), 7.70(1H,d,J=8.1Hz), 7.80(1H,d,J=7.3Hz), 7.93(1H,d,J=8.1Hz), 8.57(1H,d,J=4.4Hz), 8.63(1H,s), 9.17(1H,s).

【０１０７】

（３２－２）　工程（３２－１）の化合物１．２ｇ（２．８ｍｍｏｌ）をメタノール１０ｍｌに溶解した。４規定塩酸／ジオキサン溶液２０ｍｌを加え、室温で１．５時間撹拌した。希水酸化ナトリウム水溶液にあけた後、クロロホルム６０ｍｌで３回抽出した。飽和食塩水で２回洗浄後、無水硫酸マグネシウムで乾燥し、濃縮して０．８８ｇの結晶を得た。ついでエタノール１６ｍｌで再結晶を行い、Ｎ－（２－アミノフェニル）－４－［（ピリジン－３－イル）メトキシカルボニル］アミノメチルベンズアミド６６８ｍｇ（収率７３％）を得た。

【０１０８】

mp. 159-160℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.28(2H,d,J=5.9Hz), 4.86(2H,s), 5.10(2H,s), 6.60(1H,t,J=7.3Hz), 6.78(1H,d,J=7Hz), 6.97(1H,t,J=7Hz), 7.17(1H,d,J=8Hz), 7.3-7.5(3H,m), 7.78(1H,d,J=8Hz), 7.93(2H,d,J=8Hz), 8.53(1H,d,J=3.7Hz), 8.59(1H,s), 9.61(1H,s).

IR(KBr)cm-1: 3295,1648,1541,1508,1457,1309,1183,742.

実施例３２に記載と同様の方法により、実施例３３から実施例５３の化合物を合成した。以下に、化合物の融点（mp.）、1H NMR、IRの測定値を示す。

【0109】

実施例33

N－（2－アミノフェニル）－4－（ベンジルオキシカルボニル）アミノメチルベンズアミド（表－1：化合物番号11）

mp. 174-178℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.28(2H,d,5.9), 4.89(2H,br. s), 5.06(2H,s), 6.59(1H,dd,7.3,8.1), 6.78(1H,d,8.1), 6.97(1H,dd,7.3,8.1), 7.16(1H,d,7.3),7.3-7.4(6H,m), 7.93(3H,m), 9.63(1H,s).

IR(KBr)cm-1: 3332,1687,1652,1536,1456,1279,747.

【0110】

実施例34

N－（2－アミノフェニル）－4－［（4－（イミダゾール－1－イル）ベンジル）オキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号47）

mp. 195-198℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.29(2H,d,J=6.6Hz), 4.88(2H,s), 5.10(2H,s), 6.60-6.63(1H,m), 6.78(1H,d,J=8.1Hz), 6.97(1H,t,J=7.3Hz), 7.11(1H,s), 7.16(1H,d,J=7.3Hz), 7.37(2H,d,J=8.1Hz), 7.49(2H,d,J=8.8Hz), 7.66(2H,d,J=8.1Hz), 7.74(1H,s), 7.92-7.96(3H,m), 8.25(1H,s), 9.62(1H,s).

【0111】

実施例35

N－（2－アミノフェニル）－4－［（ピリジン－2－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号51）

mp. 166-167℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.30(2H,d,5.9), 4.88(2H,br.s), 5.12(2H,s), 6.60(1H,dd,7.3,8.1), 6.78(1H,d,8.1), 6.97(1H,ddd,1.5,7.3,8.1), 7.16(1H,d,7.3), 7.33(1H,dd,3.7,7.3), 7.40(3H,d,8.1), 7.83(1H,ddd,1.5,7.3,8.1), 7.94(2H,d,8.1), 8.03(1H,t,5.9), 8.55(1H,d,5.1), 9.62(1H,br.s).

IR(KBr)cm-1: 3334,1694,1632,158,1276,755.

【0112】

実施例３６

Ｎ－（２－アミノフェニル）－４－［２－（ピリジン－２－イル）エトキシカルボニル］アミノメチルベンズアミド（表－１：化合物番号５２）

mp. 146-148℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.04(2H,t,6.6), 4.23(2H,d,5.9), 4.36(2H,t,6.6), 4.88(2H,br.s), 6.60(1H,dd,7.3,8.1), 6.78(1H,d,8.1), 6.97(1H,dd,7.3,8.1), 7.15-7.30(3H,m), 7.34(2H,d,8.1), 7.69-7.77(2H,m), 7.92(2H,d,7.3), 8.50(1H,d,4.4), 9.62(1H,br.s).

IR(KBr)cm-1: 3330,1690,1633,1594,1524,1277,760.

【０１１３】

実施例３７

Ｎ－（２－アミノフェニル）－４－［（６－メチルピリジン－２－イル）メトキシカルボニル］アミノメチルベンズアミド（表－１：化合物番号５９）

mp. 138℃.

1H NMR(270MHz, DMSO-d6) δ ppm : 2.47 (3H,s), 4.30 (2H,d,J=5.9), 5.07 (4H,s), 6.63 (1H,t,J=8.1), 6.80 (1H,d,J=7.34), 6.98 (1H,t,J=8.1), 7.18 (3H,d,J=7.3), 7.40 (2H,d,J=8.1), 7.71 (1H,t,J=8.1), 7.94 (2H d,J=8.1), 8.03 (1H,t,J=5.9), 9.66 (1H,s)

IR(KBr)cm-1: 1259,1634,1693,3335.

【０１１４】

実施例３８

Ｎ－（２－アミノフェニル）－４－［（２－ピリジン－３－イル）エトキシカルボニル］アミノメチルベンズアミド（表－１：化合物番号８３）

mp. 120-125℃.

1H NMR(270MHz, DMSO-d6) δ ppm : 2.91 (2H,t,J=6.60), 4.22 (4H,t,J=6.6), 4.89 (2H,s), 6.55-6.63 (1H,m), 6.78 (1H,dd,J=8.1,1.5), 6.97 (1H,t,J=6.6), 7.17 (1H,d,J=6.6), 7.33 (3H,d,J=8.1), 7.69 (1H,d,J=8.1), 7.79 (1H,t,J=6.6), 7.93 (2H,d,J=8.0), 8.43-8.49 (2H,m), 9.62 (1H,s).

IR(KBr)cm-1: 1260,1655,1705,3234.

【0115】

実施例39

N－（2－アミノフェニル）－4－［3－（ピリジン－3－イル）プロピルオキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号84）

mp. 121-124℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 1.83-1.94(2H,m), 2.67(2H,t,7.3), 3.98(2H,t,6.6), 4.26(2H,d,5.9), 4.89(2H,br.s), 6.60(1H,dd,8.1,8.1), 6.78(1H,d,7.3), 6.97(1H,ddd,1.5,7.3,8.1), 7.16(1H,d,8.1), 7.29-7.33(1H,m), 7.37(1H,d,8.1), 7.64(1H,d,8.1), 7.81(1H,dd,5.9,6.6), 7.94(2H,d,8.1), 8.40-8.44(2H,m), 9.63(1H,br.s).

IR(KBr)cm-1: 3348,1696,1635,1523,1458,1302,1272,1141,1019,754,713.

【0116】

実施例40

N－（2－アミノフェニル）－4－［（2－メチルピリジン－3－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号92）

mp. 164-165℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.49(3H,s), 4.28(2H,d,J=6.6), 4.89(2H,s), 5.10(2H,s), 6.60(1H,t,J=6.6), 6.78(1H,d,J=8.1), 6.9(1H,t,J=7.3), 7.17(1H,d,J=7.3), 7.21-7.26(1H,m), 7.37(2H,d,J=8.1), 7.68(1H,d,J=6.6), 7.92-8.00(3H,m), 8.39(1H,d,J=4.4), 9.62(1H,s)

IR(KBr)cm-1: 1260,1630,1719,3332.

【0117】

実施例41

N－（2－アミノフェニル）－4－［（6－メチルピリジン－3－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号94）

mp. 164-165℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.46(3H,s),4.27(2H,d,J=6.6), 4.88(2H,s), 5.05(2H,s), 6.59(1H,dt,J=8.1,1.5), 6.78(1H,dd,J=8.1,1.5), 6.97(1H,dt,J=7.3,1.5), 7.17(1H,d,J=7.3), 7.26(1H d,J=8.1), 7.36(2H,d,J=8.1), 7.67(1H,d

d,J=8.1,2.2), 7.93(3H,d,J=8.1), 8.45(1H,d,J=1.5), 9.62(1H,s).

IR(KBr)cm-1: 1260,1632,1701,3293.

【0118】

実施例42

N－（2－アミノフェニル）－4－［（2－クロロピリジン－3－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号106）

mp. 159-169℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.30(2H,d,J=5.9), 5.00(2H,s), 5.13(2H,s), 6.61(1H,t,J=7.34), 6.79(1H,dd,J=8.1,1.5), 6.98(1H,dt,J=7.3,1.5), 7.17(1H,d,J=6.6), 7.39(2H,d,J=8.8), 7.47-7.52(1H,m), 7.91-7.96(3H,m), 8.08(1H,t,J=5.9), 8.40(1H,dd,J=4.4,1.5), 9.64(1H,s).

IR(KBr)cm-1: 1273,1632,1702,3340.

【0119】

実施例43

N－（2－アミノフェニル）－4－［（6－クロロピリジン－3－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号108）

mp. 180-185℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.24(2H,d,J=5.9), 4.89(2H,br.s), 5.10(2H,s), 6.60(1H,t,J=7.3), 6.78(1H,d,J=8.1), 6.97(1H,dt,J=8.1,1.5), 7.16(1H,d,J=6.6), 7.37(2H,d,J=8.1), 7.56(1H,d,J=8.1), 7.85-8.02(4H,m), 8.44(1H,d,J=2.2), 9.62(1H,s).

IR(KBr)cm-1: 1271,1533,1696,3282,3346.

【0120】

実施例44

N－（2－アミノフェニル）－4－［（ピリジン－4－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号121）

mp. 180-183℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.30(2H,d,6.6), 4.89(2H,s), 5.12(2H,s), 6.60(1H,dd,7.3,7.3), 6.78(1H,dd,1.5,7.3), 6.97(1H,ddd,1.5,7.3,8.1), 7.16(1

H,d,7.3), 7.34(2H,d,5.9), 7.39(2H,d,8.1), 7.94(2H,d,8.1), 8.09(1H,t,5.9), 8.57(1H,d), 9.64(1H,br.s).

IR(KBr)cm-1: 3394,3290,1711,1645,1624,1535,1504,1321,1251,1138,1049,763.

【0121】

実施例45

N－（2－アミノフェニル）－4－［2－（チオフェン－3－イル）エトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号136）

mp.128-138℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.90(2H,t,J=7.3), 4.17-4.26(4H,m), 4.89(2H,s), 6.60(1H,t,J=8.1), 6.78(1H,d,J=6.6), 6.97(1H,t,J=7.3), 7.06(1H,d,J=5.1), 7.17(1H,d,J=7.3), 7.26(1H,s), 7.36(2H,d,J=8.1), 7.47(1H,t,J=2.2), 7.81(1H,t,J=5.9), 7.93(2H,d,J=8.1), 9.63(1H,s).

IR(KBr)cm-1: 1252,1638,1716,3314.

【0122】

実施例46

N－（2－アミノフェニル）－4－［（3－フェニルオキサゾール－5－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号141）

mp. 192-195℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.30(2H,d,J=5.9), 4.89(2H,s), 5.25(2H,s), 6.60(1H,t,J=6.6), 6.68(1H,d,J=8.1), 6.94(1H,t,J=7.3), 7.09(1H,s), 7.16(1H,d,J=7.3), 7.39(2H,d,J=8.1), 7.51(4H,d,J=2.2), 7.87-7.96(5H,m), 8.12(1H,t,J=5.9), 9.63(1H,s).

IR(KBr)cm-1: 1262,1630,1718,3292.

【0123】

実施例47

N－（2－アミノフェニル）－4－［（チアゾール－5－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号147）

mp. 168-175℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.28(2H,d,5.9), 4.91(2H,br.s), 5.30(2H,s),

6.60(1H,dd,7.3,7.3), 6.78(1H,d,8.1), 6.97(1H,dd,7.3,8.1), 7.16(1H,d,7.3), 7.36(2H,d,8.1), 7.91-8.00(4H,m), 9.09(1H,s), 9.63(1H,s).

IR(KBr)cm-1: 3346(br.),1697,1636,1525,1456,1271,873,753.

【0124】

実施例48

N-(2-アミノフェニル)-4-[2-(4-メチルチアゾール-5-イル)エトキシカルボニル]アミノメチルベンズアミド(表-1:化合物番号148)

mp. 130-133℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.32(3H,s), 3.07(2H,t,J=5.9), 4.15(2H,t,J=5.9), 4.25(2H,d,J=6.6), 4.89(2H,s), 6.60(1H,t,J=5.9), 6.78(1H,dd,J=7.3,1.5), 6.97(1H,dt,J=7.3,1.5), 7.16(1H,d,J=8.1), 7.35(2H,d,J=8.1), 7.83(1H,t,J=5.9), 7.94(2H,d,J=8.1), 8.85(1H,s), 9.62(1H,s).

IR(KBr)cm-1: 1270,1635,1691,3350.

【0125】

実施例49

N-(2-アミノフェニル)-4-[(1-メチルピペリジン-3-イル)メトキシカルボニル]アミノメチルベンズアミド(表-1:化合物番号152)

mp. 130-135℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 1.49-1.78(3H,m), 1.83-2.01(3H,m), 2.30(3H,s), 2.85(2H,t), 3.74-3.94(2H,m), 4.25(2H,d,J=5.8), 6.55-6.62(3H,m), 6.78(1H,d,J=8.1), 6.97(1H,t,J=7.3), 7.16(1H,d,J=8.1), 7.37(2H,d,J=8.1), 7.79(1H,t,J=6.6), 7.93(2H,d,J=8.0), 9.66(1H,s).

IR(KBr)cm-1: 1263,1648,1702,2722,3323.

【0126】

実施例50

N-(2-アミノフェニル)-4-[(4-メチルピペラジン-1-イル)メトキシカルボニル]アミノメチルベンズアミド(表-1:化合物番号153)

mp. 145-155℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 1.73(2H,t,J=6.6), 2.36-2.63(13H, m), 4.00

(2H,t,J=6.6), 4.30(2H,d,J=5.8), 6.55-6.63(4H,m), 6.78(1H,d,J=6.6), 6.97(1H,t,J=7.3), 7.16(1H,d,J=7.3), 7.37(2H,d,J=8.7), 7.73(1H,t,J=5.9), 7.94(2H,d,J=8.0), 9.66(1H,s).

IR(KBr)cm-1: 1262,1701,2706,3341.

【0127】

実施例51

N－（2－アミノフェニル）－4－［（テトラヒドロフラン－3－イル）メトキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号155）

1H NMR(DMSO-d6) δ ppm: 1.50-1.60(1H,m), 1.88-2.00(1H,m), 2.44-2.54(1H,m), 3.41-3.47(1H,m), 3.56-3.77(3H,m), 3.85-4.04(2H,m), 4.25(2H,d,J=5.9Hz), 4.89(2H,s), 6.60(1H,dd,J=7.3,7.3Hz), 6.78(1H,d,J=8.1), 6.97(1H,dd,J=7.3, 8.1Hz), 7.17(1H,d,J=8.1), 7.37(2H,d,J=8.1Hz), 7.81(1H,t,J=5.9Hz), 7.94(2H,d,J=8.1), 9.62(1H,br.s).

IR(KBr)cm-1: 3349,1695,1635,1523,1457,1259,754.

【0128】

実施例52

N－（2－アミノフェニル）－4－（フェノキシカルボニル）アミノメチルベンズアミド（表－1：化合物番号12）

mp.174-175℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.36(2H,d,5.9), 4.90(2H,br.s), 6.60(1H,dd, 7.3,7.3), 6.77(1H,dd,7.3,7.3), 6.98(1H,ddd,1.5,7.3,7.3), 7.05-7.24(4H,m), 7.39-7.46(4H,m), 7.97(2H,d,8.1), 8.41(1H,t,5.9), 9.65(1H,br.s).

IR(KBr)cm-1: 3443,3362,3313,1732,1706,1636,1527,1493,1458,1305,1217,748.

【0129】

実施例53

N－（2－アミノフェニル）－4－［（ピリジン－3－イル）オキシカルボニル］アミノメチルベンズアミド（表－1：化合物番号81）

mp. 209℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.38(2H,d,6.6), 4.90(2H,br.s), 6.55-6.63(1

H,m), 6.78(1H,d,8.1), 7.00(1H,dd,7.3,7.3), 7.17(1H,d,8.8), 7.37-7.47(3H,m), 7.64(1H,d,8.8), 7.97(2H,d,8.1), 8.43(2H,d,3.1), 8.59(1H,t,5.9), 9.66(1H,br.s).

【0130】

実施例54

N－（2－アミノフェニル）－4－［（ピリジン－3－イル）メトキシチオカルボニル］アミノメチルベンズアミド（表－1：化合物番号86）

（54－1） 3－ピリジルメタノール20mg（0．18mmol）を5mlの乾燥THFに溶解し、N，N'－チオカルボニルジイミダゾール30mg（0．16mmol）を室温で加えた。終夜撹拌した後、実施例1の工程（1－4）の化合物50mg（0．14mmol）を加えた。

【0131】

室温で一夜放置後、クロロホルム100mlを加え、水20ml で3回洗浄した。ついで飽和食塩水で洗浄後、無水硫酸マグネシウムで乾燥した。溶媒を減圧留去後シリカゲルカラムクロマトグラフィー（クロロホルム：メタノール＝30：1）で精製し、N－［2－（N－tert－ブトキシカルボニル）アミノフェニル］－4－［（ピリジン－3－イル）メトキシチオカルボニル］アミノメチルベンズアミド70mg（収率88%）をアモルファスとして得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.45(9H,s), 4.73(2H,d,J=5.9Hz), 5.52(2H,s), 6.73-7.33(3H,m), 7.35-7.43(2H,m), 7.58-7.95(5H,m), 8.14-8.65(3H,m), 9.80(1H,s), 9.91(1H,t).

【0132】

（54－2） 工程（54－1）の化合物50mg（0．10mmol）をメタノール3ml に溶解した。4規定塩酸／ジオキサン溶液3ml を加え、室温で1．5時間撹拌した。希水酸化ナトリウム水溶液にあけ塩酸を中和した後、クロロホルム10ml で3回抽出した。飽和食塩水で2回洗浄後、無水硫酸マグネシウムで乾燥し、濃縮して34mg（収率87%）のN－（2－アミノフェニル）－4－［（ピリジン－3－イル）メトキシチオカルボニル］アミノメチルベンズアミドを得た。

mp. 154-156℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.73(2H,d,J=5.9Hz), 4.88(2H,s), 5.52(2H,s), 6.60(1H,t,J=7.3Hz), 6.77(1H,d,J=8.1Hz), 6.96(1H,t,J=8.1Hz), 7.16(1H,d,J=7.3Hz), 7.29-7.41(3H,m), 7.83-7.95(3H,m), 8.50-8.56(1H,m), 8.65(1H,s), 9.62(1H,s), 9.93(1H,t).

【0133】

実施例55

N－（2－アミノフェニル）－4－［N'－（ピリジン－3－イルメチル）ウレイドメチル］ベンズアミド（表－1：化合物番号88）の合成

（５５－１）３－ピコリルアミン（０．２８ｇ，２．６ｍｍｏｌ）のＴＨＦ（１０ｍｌ）溶液に室温でＮ，Ｎ’－カルボニルジイミダゾール（０．４２ｇ，２．４ｍｍｏｌ）を加え、１時間撹拌した。この溶液に室温で実施例１の工程（１－４）で得られた化合物（０．５８ｇ，１．８ｍｍｏｌ）を加え、３時間撹拌した後、一晩放置した。

【０１３４】

水を加え希釈した後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得た残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル－メタノール＝１０：１）で精製して、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノ］フェニル－４－［Ｎ’－（ピリジン－３－イルメチル）ウレイドメチル］ベンズアミド（０．７７ｇ，９０％）を白色アモルファス状固体として得た。

1H NMR(270MHz, CDCl3) δ ppm: 1.46(9H,s), 4.20(2H,d,5.1), 4.28(2H,d,4.3), 6.1-6.3(2H,bm), 7.0-7.25(4H,m), 7.33(1H,d,7.3), 7.49-7.54(2H,m), 7.58-7.64(3H,m), 7.75(1H,s), 8.28(1H,br.s), 8.39(1H,d,5.1), 9.65(1H,br.s).

【０１３５】

（５５－２）　工程（５５－１）で得た化合物（０．６３ｇ，１．３２ｍｍｏｌ）のジオキサン（４ｍｌ）－メタノール（２ｍｌ）溶液に４規定塩酸－ジオキサン（４ｍｌ）を加え、室温２時間で撹拌した。飽和重曹水を加えた後、酢酸エチル－メチルエチルケトンで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得た残渣をジイソプロピルエーテルで洗浄することにより、Ｎ－（２－アミノフェニル）－４－［Ｎ’－（ピリジン－３－イルメチル）ウレイドメチル］ベンズアミド（０．３７ｇ，７４．７％）を褐色固体として得た。

【０１３６】

mp. 167-175℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.27(2H,d,5.9), 4.31(2H,d,5.9), 4.89(2H,br.s), 6.57-6.63(3H,m), 6.78(1H,d,8.1), 6.97(1H,dd,7.3,8.1), 7.17(1H,d,7.3), 7.32-7.38(3H,m), 7.66(1H,d,8.1), 7.93(2H,d,8.1), 8.44(1H,d,5.1), 8.49(1H,d,2.1), 9.63(1H,br.s).

IR(KBr)cm-1: 3344,3241,1645,1560,1527,1505,1283,751,708.

【0137】

実施例55に記載と同様の方法により、実施例56から実施例59の化合物を合成した。以下に、化合物の融点（mp.）、1H NMR、IRの測定値を示す。

実施例56

N－（2－アミノフェニル）－4－［N'－（3－アミノフェニル）ウレイドメチル］ベンズアミド（表－1：化合物番号24）

mp. 206-208℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.35(2H,d,J=5.9Hz), 4.93(4H,br.s), 6.13(1H,d,J=7.3Hz), 6.51-6.62(3H,m), 6.74-6.98(3H,m), 7.12-7.18(1H,m), 7.41(2H,d,J=8.1Hz), 7.94(2H,d,J=8.1Hz), 8.28(1H,s), 9.61(1H,s).

【0138】

実施例57

N－（2－アミノフェニル）－4－［N'－（ピリジン－3－イル）ウレイドメチル］ベンズアミド（表－1：化合物番号87）

mp. 187-190℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.39(2H,d,5.9), 4.89(2H,br.s), 6.59(1H,d,7.3,7.3), 6.77(1H,d,6.6), 6.88(1H,t,5.9), 6.97(1H,ddd,1.5,6.6,7.3), 7.16(1H,d,8.1), 7.26(1H,dd,4.4,8.1), 7.42(2H,d,8.8), 7.95(2H,d,8.1), 7.89-7.96(1H,m), 8.12(1H,dd,1.5,4.4), 8.56(1H,d,3.0), 8.85(1H,s), 9.62(1H,s).

IR(KBr)cm-1: 3248,1663,1541,1423,1280,1054.

【0139】

実施例58

N－（2－アミノフェニル）－4－［N'－（3－アミノフェニル）チオウレイドメチル］ベンズアミド（表－1：化合物番号25）

mp. 123℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.80(2H,d,J=5.1Hz), 4.87(2H,s), 5.12(2H,s), 6.36(1H,dd,J=1.5,8.1Hz), 6.48-6.63(3H,m), 6.78(1H,d,J=6.6Hz), 6.94-7.00(2H,m), 7.17(1H,d,J=8.1Hz), 7.42(2H,d,J=8.1Hz), 7.92-8.01(3H,m), 9.46(1

H,s), 9.61(1H,s).

【0140】

実施例59

N－（2－アミノフェニル）－4－［N'－（3－ニトロフェニル）チオウレイドメチル］ベンズアミド（表－1：化合物番号20）

mp. 160℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.87(2H,d,J=5.1Hz), 7.27-7.33(3H,m), 7.46-7.63(5H,m), 7.89-7.95(2H,m), 8.05(2H,d,J=8.1Hz), 8.70(1H,s), 8.84(1H,t,J=8.9Hz), 10.37(1H,s).

【0141】

実施例60

N－（2－アミノフェニル）－4－［2－（N－（ピリジン－3－イルアセチル）アミノ）エチル］ベンズアミド（表－1：化合物番号77）の合成

（60－1） テレフタルアルデヒド酸3．40g（22．6mmol）のトルエン（25ml）懸濁液にチオニルクロライド（4ml）を加え、2時間加熱撹拌した。放冷後、溶媒を留去し得られた残渣をTHF（50ml）に溶解し、酸クロライドを調製した。実施例1の工程（1－2）の化合物4．16g（20．0mmol）のTHF（10ml）溶液にトリエチルアミン（6ml，42．8mmol）を加え、さらに先に調製した酸クロライドを氷冷下30分かけて滴下した。

【0142】

5時間撹拌後、飽和重曹水を加え、酢酸エチルで抽出した。有機層を飽和食塩水洗浄後、乾燥、溶媒を留去して得られた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム→クロロホルム：酢酸エチル＝10：1）で精製し、N－［2－（N－tert－ブトキシカルボニル）アミノフェニル］－4－ホルミルベンズアミド3．42g（収率50．2%）を淡褐色固体として得た。

1H NMR(CDCl3) δ ppm: 1.52(9H,s), 6.77(1H,br.s), 7.16-7.18(2H,m), 7.23-7.26(1H,m), 7.88(1H,d,J=8.8Hz), 7.98(2H,d,J=8.8Hz), 8.13(2H,d,J=8.8Hz), 9.57(1H,br.s), 10.11(1H,br.s).

IR(KBr)cm-1: 3326,3251,1707,1696,1659,1603,1165.

【0143】

（60－2） 工程（60－1）で得られた化合物3．0g（8．82mmol）およびエトキシカルボニルメチルトリフェニルホスファイト4．5g（12．9mmol）のトルエン（10ml）懸濁液を窒素気流下80℃で、5．5時間撹拌した。放冷後、酢酸エチルで希釈した後、飽和重曹水、水、飽和食塩水で洗浄し、乾燥した。溶媒を留去して得られた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム：酢酸エチル＝20：1）で精製し、エチル 4－（N－2－（N－tert－ブトキシカルボニル）アミノフェニル）アミノカルボニルシンナメート3．3g（収率91．1％）を黄色アモルファス状固体として得た。

1H NMR(CDCl3) δ ppm: 1.35(3H,t,J=7.3Hz), 1.52(9H,s), 4.28(2H,q,J=7.3Hz), 6.52(1H,d,J=15.1Hz), 6.80(1H,br.s), 7.16-7.25(3H,m), 7.61(2H,d,J=8.1Hz), 7.71(1H,d,J=15.1Hz), 7.82(1H,d,7.3), 7.98(2H,d,J=8.1Hz), 9.34(1H,br.s).

【0144】

（60－3） 工程（60－2）で得られた化合物2．50g（6．09mmol）のTHF（30ml）－メタノール（40ml）溶液に窒素気流下10％Pd／C（含水，0．5g）を加えた後、水素気流下30分間撹拌した。窒素置換した後、触媒を濾過した。濾液の溶媒を留去して得た残渣にジイソプロピルエーテルを加え、析出した固体を濾取、乾燥することによりN－［2－（N－tert－ブトキシカルボニル）アミノフェニル］－4－（2－エトキシカルボニル）エチルベンズアミド2．23g（収率88．8％）を白色固体として得た。

1H NMR(CDCl3) δ ppm: 1.25(3H,t,J=7.3Hz), 1.52(9H,s), 2.65(2H,t,J=7.3Hz), 3.02(2H,t,J=7.3Hz), 4.13(2H,q,J=7.3Hz), 6.77(1H,br.s), 7.16-7.33(5H,m), 7.78(1H,d,J=8.1Hz), 7.89(2H,d,J=8.8Hz), 9.06(1H,br.s).

【0145】

（60－4） 工程（60－3）で得られた化合物2．21g（5．36mmol）のメタノール（10ml）－水（15ml）懸濁液に水酸化リチウム1水和物0．37g（8．82mmol）を加え、40℃で3時間撹拌した。放冷後1

０％塩酸水溶液を加え、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣にジイソプロピルエーテルを加え、析出した固体を濾取、乾燥することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－（２－カルボキシエチル）ベンズアミド１．８７ｇ（収率９０．８％）を白色固体として得た。

1H NMR(DMSO-d6) δ ppm: 1.45(9H,s), 2.59(2H,t,J=7.3Hz), 2.91(2H,t,J=7.3Hz), 7.13-7.20(2H,m), 7.40(2H,d,J=8.1Hz), 7.54(2H,dd,J=7.3,2.1), 7.88(2H,d,J=8.1Hz), 8.66(1H,br s), 8.66(1H,br s), 9.79(1H,br s).

【０１４６】

（６０－５）　工程（６０－４）で得られた化合物０．１２ｇ（０．３ｍｍｏｌ）のベンゼン（５ｍｌ）懸濁液にトリエチルアミン０．１ｍｌ（０．７ｍｍｏｌ）およびモレキュラーシーブ４Ａ０．３ｇを加え、窒素気流下０．５時間撹拌した。この溶液にジフェニルホスホリルアジド０．１５ｍｌ（０．７ｍｍｏｌ）を加え、２時間加熱還流した。放冷後、ベンジルアルコール０．４ｍｌ（３．８ｍｍｏｌ）を加え、さらに２．５時間加熱還流した。酢酸エチルで希釈した後、水、飽和食塩水で洗浄した。

【０１４７】

有機層を乾燥後、溶媒を留去して得られた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム：酢酸エチル＝４：１）で精製することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－（Ｎ－ベンジルオキシカルボニル）アミノエチルベンズアミド１２９ｍｇ（８８％）を無色油状物として得た。

1H NMR(CDCl3) δ ppm: 1.51(9H,s), 2.89(2H,t,J=7.3Hz), 3.45-3.54(2H,m), 4.8(1H,m), 5.10(2H,s), 6.76(1H,br.s), 7.20-7.38(10H,m), 7.79(1H,d,J=8.8Hz), 7.89(2H,d,J=8.1Hz), 9.10(1H,br.s).

【０１４８】

（６０－６）　工程（６０－５）で得られた化合物１２９ｍｇ（０．２６ｍｍｏｌ）のメタノール（１０ｍｌ）溶液に窒素気流下１０％Ｐｄ／Ｃ（含水，０．０５ｇ）を加え、水素気流下２時間撹拌した。触媒を留去した後、乾燥することに

より得られた残渣をジクロロメタン（５ｍｌ）に溶解した。この溶液に３－ピリジン酢酸塩酸塩０．１８ｇ（１．０４ｍｍｏｌ）を加え、さらにトリエチルアミン０．２８ｇ（２．０ｍｍｏｌ）を加えて氷冷した。氷冷下、２－クロロ－Ｎ，Ｎ’－ジメチルイミダゾリニウムクロライド０．１７ｇ（１．０ｍｍｏｌ）を加え、２時間撹拌した。飽和重曹水を加えた後、クロロホルムで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得た残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル：メタノール＝１０：１）で精製することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－［２－（Ｎ－（ピリジン－３－イルアセチル）アミノ）エチル］ベンズアミド５０ｍｇ（収率４０％）を無色油状物として得た。

【０１４９】

1H NMR(CDCl3) δ ppm: 1.48(9H,s), 2.80(2H,t,J=6.6Hz), 3.42(2H,m), 3.52(2H,s), 6.33(1H,t-like,J=5.9Hz), 7.09(2H,d,J=8.1Hz), 7.14-7.20(2H,m), 7.24(1H,dd,J=4.4,7.3Hz), 7.41(1H,dd,J=3.7,5.9Hz), 7.50(1H,s), 7.58(1H,dd,J=1.5,5.9Hz), 7.69(1H,dd,J=3.7,5.9Hz), 7.75(2H,d,J=8.1Hz), 8.22(1H,d,J=2.1Hz), 8.44(1H,dd,J=1.5,4.4Hz), 9.49(1H,br.s).

【０１５０】

（６０－７）　工程（６０－６）の化合物５０ｍｇ（０．１０ｍｍｏｌ）のジオキサン（２ｍｌ）－メタノール（１ｍｌ）溶液に４規定塩酸－ジオキサン（２ｍｌ）を加え、室温で２．５時間撹拌した。飽和重曹水を加えた後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣を乾燥することにより、Ｎ－（２－アミノフェニル）－４－［２－（Ｎ－（ピリジン－３－イルアセチル）アミノ）エチル］ベンズアミド２２ｍｇ（収率５９％）をアモルファス状固体として得た。

【０１５１】

1H NMR(DMSO-d6) δ ppm: 2.7-2.9(4H,m), 3.42(2H,s), 4.89(2H,br.s), 6.60(1H,dd,J=7.3,7.3Hz), 6.78(1H,d,J=7.3Hz), 6.97(1H,dd,J=7.3,7.3Hz), 7.16(1H,d,J=7.3Hz), 7.29-7.32(3H,m), 7.59(1H,d,J=8.1Hz), 7.89(1H,d,J=8.1Hz), 8.22(1H,t-like), 8.41-8.43(2H,m), 9.62(1H,br.s).

【０１５２】

実施例６１

Ｎ－（２－アミノフェニル）－４－［２－（Ｎ－（３－ピコリル）アミノカルボニル）エチル］ベンズアミド（表－１：化合物番号８０）の合成

（６１－１）　実施例６０の工程（６０－４）で得られた化合物０．５８ｇ（１．５ｍｍｏｌ）のジクロロメタン（５ｍｌ）懸濁液に、３－ピコリルアミン０．２２ｇ（２．０ｍｍｏｌ）およびトリエチルアミン０．５６ｍｌ（４．０ｍｍｏｌ）を加えた。氷冷下、２－クロロ－Ｎ，Ｎ’－ジメチルイミダゾリニウムクロライド０．３９ｇ（２．０ｍｍｏｌ）のジクロロメタン（５ｍｌ）溶液を加え、１．５時間撹拌した。飽和重曹水を加えた後、クロロホルムで抽出した。

【０１５３】

有機層を水、飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣をシリカゲルカラムクロマトグラフィー（クロロホルム：メタノール：アンモニア水＝１００：１０：１）で精製することにより、Ｎ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－［２－（Ｎ－（３－ピコリル）アミノカルボニル）エチル］ベンズアミド０．７１ｇ（収率９４％）を淡褐色油状物として得た。

1H NMR(CDCl3) δ ppm: 1.45(9H,s), 2.42(2H,t,J=7.3Hz), 2.98(2H,t,J=7.3Hz), 4.32(2H,d,J=6.6Hz), 6.44(1H,t,J=6.6Hz), 7.14-7.27(5H,m), 7.48-7.57(3H,m), 7.63-7.68(3H,m), 7.90(1H,d,J=2.1Hz), 8.43(1H,dd,J=1.4,4.4Hz), 9.86(1H, br.s).

【０１５４】

（６１－２）　工程（６１－１）の化合物０．７０ｇ（１．４７ｍｍｏｌ）のジオキサン（５ｍｌ）溶液に４規定塩酸－ジオキサン（５ｍｌ）を加え、さらにメタノール（２ｍｌ）を加えて室温で２時間撹拌した。飽和重曹水を加えた後、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣にジイソプロピルエーテルを加え、析出した固体を濾取、乾燥することにより、Ｎ－（２－アミノフェニル）－４－［２－（Ｎ－（３－ピコリル）アミノカルボニル）エチル］ベンズアミド０．４２ｇ（収率７６．３％）を乳白色固

体として得た。

【0155】

mp. 168-170℃.

1H NMR(DMSO-d6) δ ppm: 2.47-2.53(2H,m), 2.93(2H,t,J=7.3Hz), 4.27(2H,d,J=5.9Hz), 4.90(2H,br.s), 6.60(1H,dd,J=7.3,7.3Hz), 6.78(1H,d,J=8.1Hz), 6.97(1H,dd,J=6.6,7.3Hz), 7.16(1H,d,J=6.6Hz), 7.28-7.35(1H,m), 7.33(2H,d,J=8.1Hz), 7.49(1H,dd,J=2.1,5.9Hz), 7.89(2H,d,J=8.1Hz), 8.39-8.44(3H,m), 9.62(1H,br.s).

IR(KBr)cm-1: 3313,1641,1523,1457,1300,748,713.

【0156】

実施例62

N－（2－アミノフェニル）－4－［（ピリジン－3－イル）メチルアミノカルボニルオキシ］メチルベンズアミド（表－1：化合物番号85）の合成

（62－1） メチル 4－ヒドロキシメチルベンゾエート（1．99g，12．0mmol）のTHF（20ml）溶液に室温でN，N'－カルボニルジイミダゾール1．78g（11．0mmol）を加え、1時間撹拌した。この溶液に室温で3－ピコリルアミン1．08g（10．0mmol）を加え、3．5時間撹拌した後、一晩放置した。これに水を加え希釈した後、酢酸エチルで抽出した。

【0157】

有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得た残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル）で精製して、N－（4－メトキシカルボニル）ベンジルオキシカルボニル－3－ピコリルアミン2．76g（収率91．9％）を白色ワックス状固体として得た。

1H NMR(CDCl3) δ ppm: 3.91(3H,s), 4.40(2H,d,J=5.9Hz), 5.18(2H,s), 5.5(1H,br s),

7.24-7.28(1H,m), 7.40(2H,d,J=8.1Hz), 7.65(1H,d,J=7.3Hz), 8.02(2H,d,J=8.8Hz), 8.50-8.53(2H,m).

【0158】

（６２－２）　工程（６２－１）の化合物２．４０ｇ（８．０ｍｍｏｌ）のメタノール（１０ｍｌ）－水（２０ｍｌ）懸濁液に、水酸化リチウム１水和物０．４２ｇ（１０．０ｍｍｏｌ）を加え、室温で５時間撹拌した。１０％塩酸水溶液を加え、酸性（ｐＨ２～４）にした後、析出した固体を濾取、乾燥することにより、Ｎ－（４－カルボキシ）ベンジルオキシカルボニル－３－ピコリルアミン１．８３ｇ（収率７９．９％）を白色固体として得た。

1H NMR(DMSO-d6) δ ppm: 4.24(2H,d,J=5.9Hz), 5.13(2H,s), 7.33-7.38(1H,m), 7.46(2H,d,J=8.1Hz), 7.94(2H,d,J=8.1Hz), 7.95-8.01(1H,m), 8.46(1H,d,J=5.1Hz), 8.49(1H,d,J=1.5Hz), 13.0(1H,br.s).

【０１５９】

（６２－３）　工程（６２－２）の化合物１．２６ｇ（４．４ｍｍｏｌ）のジクロロメタン（２０ｍｌ）懸濁液にオキザリルクロライド１．０ｍｌ（１１．４ｍｌ）を徐々に加え、更にＤＭＦを数滴加えた後室温で１０分間、さらに４０℃で３０分間撹拌した。放冷後、溶媒を留去し、更にトルエンで過剰のオキザリルクロライドを留去した。この残渣にジクロロメタン（１０ｍｌ）を加えた後、氷冷し、さらに実施例１の工程（１－２）で得られた化合物０．８３ｇ（４．０ｍｍｏｌ）のジクロロメタン（８ｍｌ）－ピリジン（８ｍｌ）溶液を滴下した後、室温まで昇温させながら７時間撹拌し、一晩放置した。

【０１６０】

飽和重曹水を加えた後、クロロホルムで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得られた残渣にトルエンを加え。さらに過剰のピリジンを共沸した。得られた残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル）で精製することによりＮ－［２－（Ｎ－ｔｅｒｔ－ブトキシカルボニル）アミノフェニル］－４－［（ピリジン－３－イル）メチルアミノカルボニルオキシ］メチルベンズアミド１．４０ｇ（収率７３．４％）を淡褐色固体として得た。

1H NMR(CDCl3) δ ppm: 1.51(9H,s), 4.40(2H,d,J=5.9Hz), 5.19(2H,s), 5.56(1H,m), 7.07(1H,br.s), 7.14-7.31(4H,m), 7.43(2H,d,J=8.1Hz), 7.65(1H,d,J=8.1Hz), 7.76(1H,d,J=7.3Hz), 7.95(2H,d,J=8.1Hz), 8.52(2H,d,J=4.1Hz), 9.32(1H,br .s).

【0161】

（62－4） 工程（62－3）の化合物1．00g（2．10mmol）のジオキサン（10ml）－メタノール（2ml）溶液に室温で4N塩酸－ジオキサン（9ml）を加えて2時間撹拌した。飽和重曹水を加えた後、酢酸エチル－メチルエチルケトン（1：1）で抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去し、得られた残渣にメタノール－ジイソプロピルエーテルを加え、生成した固体を濾取、乾燥することにより、N－（2－アミノフェニル）－4－［（ピリジン－3－イル）メチルアミノカルボニルオキシ］メチルベンズアミド0．79g（定量的）を白色固体として得た。

mp. 139-141℃

1H NMR(DMSO-d6) δ ppm: 4.25(2H,d,J=5.9Hz), 4.90(2H,s), 5.13(2H,s), 6.60(1H,dd,J=6.6,7.3Hz), 6.78(1H,d,J=7.3Hz), 6.97(1H,dd,J=6.6,7.3Hz), 7.17(1H,d,J=7.3Hz), 7.36(1H,dd,J=4.4,8.1Hz), 7.47(2H,d,J=8.1Hz), 7.67(1H,d,J=8.1Hz), 7.97(2H,d,J=7.3Hz), 7.9-8.0(1H,m), 8.46(1H,dd,J=1.5,5.1Hz), 8.49(1H,d,J=2.1Hz), 9.65(1H,br.s).

IR(KBr)cm-1: 3326(br), 1694,1637,1526,1458,1147,750,712.

【0162】

実施例63

N－（2－アミノフェニル）－4－［3－（イミダゾール－1－イル）プロピルアミノカルボニルオキシ］メチルベンズアミド（表－1：化合物番号146）の合成

実施例62に記載と同様の方法により合成した。

mp. (amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 1.80-1.89(2H,m), 2.94-3.02(2H,m), 3.98(2H,t,J=7.3Hz), 4.88(2H,s), 5.11(2H,s), 6.55-6.63(1H,m), 6.76-6.97(3H,m), 7.10-7.18(2H,m), 7.43-7.48(3H,m), 7.61(1H,s), 7.98(2H,d,J=8.1Hz), 9.66(1H,s).

【0163】

実施例64

N－（2－アミノフェニル）－4－（フェニルアセチルアミノ）ベンズアミド（表－1：化合物番号2）

（64－1） 実施例1の工程（1－2）で得た化合物（4．16g，20．0mmol）のジクロロメタン（30ml）溶液にトリエチルアミン（4．2ml，30．0mmol）を加え、さらに氷冷下、4－ニトロベンゾイルクロライド（4．00g，21．6mmol）のジクロロメタン（10ml）溶液を徐々に加えた後、7時間撹拌した。飽和重曹水を加えた後、クロロホルムで抽出した。

【0164】

有機層を1規定塩酸水溶液、飽和重曹水、飽和食塩水で洗浄した後、乾燥、溶媒を留去した。得られた残渣をジイソプロピルエーテルで洗浄することにより、N－［2－（N－tert－ブトキシカルボニルアミノ）フェニル］－4－ニトロベンズアミド（7．02g，98．3%）を淡黄色固体として得た。

1H NMR(270MHz, CDCl3) δ ppm: 1.53(9H,s), 7.17-7.29(4H,m), 7.85(1H,br.d,J=7.3Hz), 8.17(2H,d,J=8.8Hz), 8.32(2H,d,J=8.8Hz), 9.88(1H,br.s).

【0165】

（64－2） 工程（64－1）で得た化合物（6．00g，16．8mmol）のTHF（20ml）－メタノール（20ml）混合溶液に窒素気流下10%Pd／C（含水，0．6g）を加え、水素気流下1．5時間撹拌した。水素の吸収が停止した後、触媒を濾別、溶媒を留去して得られた残渣にジイソプロピルエーテルおよび酢酸エチルを加え、得られた固体を濾取、乾燥することにより、N－［2－（N－tert－ブトキシカルボニルアミノ）フェニル］－4－アミノベンズアミド（4．74g，86．2%）を白色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.46(9H.s), 5.84(2H,s), 6.61(2H,d,J=8.8Hz), 7.10-7.18(2H,m), 7.46-7.55(2H,m), 7.68(2H,d,J=8.8Hz), 8.67(1H,s), 9.49(1H,s).

【0166】

（64－3） 工程（64－2）で得た化合物1．6g（4．88mmol）の塩化メチレン溶液（15ml）に、ピリジン0．8ml（9．9mmol）、フェニルアセチルクロライド0．96ml（7．26mmol）を加え1日間撹拌

した。反応終了後、水を加え、析出した結晶を濾取し、N－［2－（N－ｔｅｒｔ－ブトキシカルボニルアミノ）フェニル］－4－（フェニルアセチルアミノ）ベンズアミド1．６６ｇ（７６％）を得た。

【０１６７】

（６４－４）　工程（６４－３）で得た化合物１ｇ（２．２４ｍｍｏｌ）のアセトニトリル溶液（２５ｍｌ）に室温でヨードトリメチルシラン０．８８ｍｌ（６．１８ｍｍｏｌ）を加え３時間撹拌した。反応終了後、溶媒を濃縮し得られた残留物をメタノールから再結晶して、N－（２－アミノフェニル）－4－（フェニルアセチルアミノ）ベンズアミド０．２９ｇ（３８％）を白色結晶として得た。

【０１６８】

mp. 232-237℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.69(2H,s),4.90(2H,s),6.60(1H,t,J=7.35),6.77(1H,d,J=7.35),6.96(1H,t,J=7.35),7.15(1H,d,J=7.35),7.22-7.35(5H,m),7.72(2H,d,J=8.80),7.95(2H,d,J=8.80),9.57(1H,s),10.43(1H,s)

IR(KBr): 2937,2764,1660,1598,1506,1459.

【０１６９】

実施例６４と同様の方法により、実施例６５から実施例７６の化合物を合成した。以下に、化合物の融点（mp.）、1H NMR、IRの測定値を示す。

実施例６５

N－（２－アミノフェニル）－4－（４－フェニルブタノイル）アミノメチルベンズアミド（表－１：化合物番号４）

1H NMR(270MHz, DMSO-d6) δ ppm: 1.91(2H,hep,J=7.3Hz), 2.37(2H,t,J=7.3Hz), 2.64(2H,t,J=7.3Hz), 5.0(2H,br.s), 6.61(1H,t,7Hz), 6.79(1H,dd,J=1.5, 8.1Hz), 6.97(1H,t,J=7Hz), 7.1-7.4(6H,m), 7.71(2H,d,J=8.8Hz), 7.94(2H,d,J=8.8Hz), 9.57(1H,s), 10.15(1H,s).

IR(KBr)cm-1: 3344,1687,1603,1542,1460,1315,1033,842,737.

【０１７０】

実施例６６

N－（２－アミノフェニル）－4－［（４－クロロフェニルアセチル）アミノ］

ベンズアミド（表－１：化合物番号１５）

mp. >250℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.72(2H,s),7.29-7.43(8H,m),7.77(2H,d,J=8.80),8.00(2H,d,J=8.80),10.29(1H,s),10.52(1H,s)

IR(KBr)cm-1: 3300,2868,1664,1638,1520.

【０１７１】

実施例６７

Ｎ－（２－アミノフェニル）－４－［（２－ニトロフェニルアセチル）アミノ］ベンズアミド塩酸塩（表－１：化合物番号１９の塩酸塩）

mp. >250℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.20(2H,s), 7.20-7.30(3H,m), 7.40-7.45(1H,m), 7.60(2H,d), 7.71-7.77(3H,m), 8.02-8.10(4H,m), 10.27(1H,br.s), 10.64(1H,br.s).

IR(KBr)cm-1: 3263,1676,1647,1518,1184,759.

【０１７２】

実施例６８

Ｎ－（２－アミノフェニル）－４－［（４－ニトロフェニルアセチル）アミノ］ベンズアミド（表－１：化合物番号２１）

mp. 222-226℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.90(2H,s),4.96(2H,br.s),6.60(1H,dt,J=1.47,6.61),6.78(1H,dd,J=1.47,6.61),6.97(1H,dt,J=1.47,6.61),7.15(1H,dd,J=1.47,6.61),7.63(2H,d,J=8.80),7.71(2H,d,J=8.80),7.95(2H,d,J=8.80),8.22(2H,d,J=8.80),9.59(1H,s),10.54(1H,s)

IR(KBr)cm-1: 3395,3334,1671,1630,1519,1346.

【０１７３】

実施例６９

Ｎ－（２－アミノフェニル）－４－［（２－アミノフェニルアセチル）アミノ］ベンズアミド（表－１：化合物番号２２）

mp. 177-182℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 3.54(2H,s), 4.88(2H,br.s), 5.09(2H,br.s), 6.55(1H,dd,6.6,7.3), 6.59(1H,dd,7.3,7.3), 6.68(1H,d,7.3), 6.78(1H,d,7.3), 6.96(2H,dd,7.3,7.3), 7.06(1H,d,6.6), 7.15(1H,d,7.3), 7.71(2H,d,8.8), 7.95(2H,d,8.8), 9.57(1H,br.s), 10.39(1H,br.s).

IR(KBr)cm-1: 3374,3256(br.),1683,1597,1503,1317,1262,1180,1153,747.

【0174】

実施例70

N－（2－アミノフェニル）－4－［（4－アミノフェニルアセチル）アミノ］ベンズアミド（表－1：化合物番号26）

mp. 219-226℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 3.46(2H,s),4.93(4H,br.s),6.52(2H,d,J=8.07),6.59(1H,dt,J=1.47,7.34),6.77(1H,dd,J=1.47,7.35),6.97(1H,dt,J=1.47,7.35),6.99(2H,d,J=8.07),7.15(1H,dd,J=1.47,7.35),7.70(2H,d,J=8.80),7.93(2H,d,J=8.80)

IR(KBr)cm-1: 3278,3032,1675,1628,1516.

【0175】

実施例71

N－（2－アミノフェニル）－4－［（4－メトキシフェニルアセチル）アミノ］ベンズアミド（表－1：化合物番号32）

mp. >250℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.62(2H,s),3.74(3H,s),6.90(2H,d,J=8.80),7.26(2H.d.J=8.80),7.30(3H,m),7.39(1H,m),7.77(2H,d,J=8.80),7.99(2H,d,J=8.80),10.26(1H,s),10.44(1H,s)

IR(KBr)cm-1: 3300,2759,1670,1638,1514,1250.

【0176】

実施例72

N－（2－アミノフェニル）－4－［（4－（N，N－ジメチルアミノ）フェニルアセチル）アミノ］ベンズアミド（表－1：化合物番号157）

mp. 140℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 3.04(6H,s),3.67(2H,s),7.16(2H,d,J=8.08),7.29-7.40(6H,m),7.76(2H,d,J=8.80),7.99(2H,d,J=8.80),10.29(1H,s),10.47(1H,s)

IR(KBr)cm-1: 3244,2951,2639,1647,1599,1507.

【0177】

実施例73

N－（2－アミノフェニル）－4－［（4－トリフルオロメチルフェニルアセチル）アミノ］ベンズアミド（表－1：化合物番号43）

mp. >250℃

1H NMR(270MHz, DMSO-d6) δ ppm: 3.84(2H,s),6.89(1H,t,J=7.35),7.00(1H,d,J=7.35),7.11(1H,t,J=7.35),7.25(1H,d,J=7.35),7.57(2H,d,J=8.80),7.71(2H,d,J=8.80),7.73(2H,d,J=8.80),7.97(2H,d,J=8.80),9.87(1H,s),10.54(1H,s)

IR(KBr)cm-1: 3260,1664,1605,1521,1327,1119.

【0178】

実施例74

N－（2－アミノフェニル）－4－［（ピリジン－2－イル）アセトアミノ］ベンズアミド2塩酸塩（表－1：化合物番号54の塩酸塩）

mp. 154-175℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.60(2H,s),7.30-7.46(3H,m),7.56(1H,d,J=7.35),7.79(2H,d,J=8.80),7.95(1H,t,J=6.61),8.01(1H,d,J=7.35),8.11(2H,d,J=8.80),8.49(1H,t,J=7.35),8.87(1H,d,J=5.14),10.46(1H,s).

【0179】

実施例75

N－（2－アミノフェニル）－4－［（ピリジン－3－イル）アセトアミノ］ベンズアミド2塩酸塩（表－1：化合物番号68の塩酸塩）

mp. 182-189℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.12(2H,s),7.29-7.59(4H,m),7.80(2H,d,J=8.80),8.05(1H,m),8.11(2H,d,J=8.80),8.57(1H,d,J=8.08),8.85(1H,d,J=5.15),8.95(1H,s),10.25(1H,s),10.48(1H,s).

【0180】

実施例76

N－（2－アミノフェニル）－4－［（3－（ピリジン－3－イル）プロパノイル）アミノ］ベンズアミド（表－1：化合物番号69）

mp. 184-186℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 2.80(2H,t,J=7.34),3.08(2H,t,J=7.34),6.87(1H,t,J=8.07),6.99(1H,dd,J=1.47,8.07),7.11(1H,dt,J=1.47,8.07),7.25(1H,d,J=8.07),7.70(2H,d,J=8.80),7.77(1H,dd,J=5.87,8.07),7.96(2H,d,J=8.80),8.22(1H,d,J=8.07),8.75(1H,d,J=1.47),9.83(1H,s),10.25(1H,s).

【０１８１】

実施例７７

Ｎ－（２－アミノフェニル）－４－（Ｎ－ベンジルアミノ）カルボニルベンズアミド（表－１：８番）の合成

（７７－１）　テレフタル酸モノメチル（１３．０ｇ，７２．２ｍｍｏｌ）のトルエン（１００ｍｌ）懸濁液にチオニルクロライド（１０ｍｌ）を室温で滴下した。８０℃で３時間攪拌した後、溶媒および過剰のチオニルクロライドを留去した。得られた残渣をジオキサン（１００ｍｌ）に懸濁させた後、２－ニトロアニリン（９．９８ｇ，７２．２ｍｍｏｌ）を加え、４時間加熱還流した。

【０１８２】

冷却後、溶媒を留去し、得られた残渣をメタノールで洗浄することにより、Ｎ－（２－ニトロフェニル）－４－メトキシカルボニルベンズアミド（２０．３ｇ，収率９３．７％）を黄色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 3.91(3H,s), 7.43-7.49(1H,m), 7.76-7.78(2H,m), 8.03(1H,d,J=8.1), 8.08(2H,d,J=8.8Hz), 8.14(2H,d,J=8.8Hz), 10.94(1H,s).

【０１８３】

（７７－２）　工程（７７－１）で得られた化合物（４．２４ｇ，１４．１２ｍｍｏｌ）のＴＨＦ（５０ｍｌ）－メタノール（５０ｍｌ）混合溶液に、窒素気流下１０％Ｐｄ／Ｃ（０．４ｇ）を加えた後、水素気流下で１．５時間攪拌した。触媒をろ過後、溶媒を留去し、得られた残渣をメタノールで洗浄することによりＮ－（２－アミノフェニル）－４－メトキシカルボニルベンズアミド（３．４ｇ，収率８７．５％）を淡黄色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 3.90(3H,s), 4.95(2H,s), 6.60(1H,dd,J=7.3,8.1), 6.78(1H,d,J=7.3), 6.99(1H,dd,J=7.3,7.3), 7.17(1H,d,J=7.3), 8.08(2H,

d,J=8.1), 8.11(2H,d,J=8.1), 9.85(1H,s)

【0184】

（77－3） 工程（77－2）で得られた化合物（2．71g，10．0mmol）のジオキサン（100ml）－水（50ml）溶液に5％水酸化ナトリウム水溶液を氷冷下で加えた後、さらにジ－tert－ブチルジカーボネート（2．62g，12．0mmol）のジオキサン（40ml）溶液を滴下した。室温で4時間撹拌後、一晩放置した。飽和食塩水及び酢酸エチルを加え二層に分離した後、水層を酢酸エチルで抽出した。有機層を飽和食塩水洗浄した後、乾燥、溶媒を留去して得られた残渣をメタノールで洗浄することにより、N－［2－（N－tert－ブトキシカルボニル）アミノ］フェニル－4－メトキシカルボニルベンズアミド（3．54g，95．7％）を淡褐色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.44(9H,s), 3.90(3H,s), 7.12-7.24(2H,m), 7.55-7.58(2H,m), 8.09(2H,d,J=8.8Hz), 8.10(2H,d,J=8.8Hz), 8.72(1H,s), 10.00(1H,s).

【0185】

（77－4） 工程（77－3）で得た化合物（3．00g，8．10mmol）のメタノール（50ml）－0．5規定水酸化リチウム水溶液（25ml）懸濁液を40℃で5時間加温撹拌した。メタノールを留去した後、得られた残渣に1規定塩酸水溶液を加え、さらに酢酸エチルで抽出した。有機層を少量の水及び飽和食塩水で洗浄した後、乾燥した。溶媒を留去して得られた残渣をメタノールで洗浄することにより、テレフタル酸 モノ－2－（N－tert－ブトキシカルボニル）アミノアニリド（2．24g，77．6％）を淡褐色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.45(9H,s), 7.12-7.21(2H,m), 7.53-7.58(2H,m), 8.06(2H,d,J=8.8Hz), 8.10(2H,d,J=8.8Hz), 8.71(1H,s), 9.97(1H,s).

【0186】

（77－5） 工程（77－4）で得た化合物（0．20g，0．56mmol）のジクロロメタン（4ml）懸濁液にベンジルアミン（0．14g，1．3mmol）を加え、さらにトリエチルアミン（0．21ml，1．5mmol）を

加えた。この溶液に氷冷下２－クロロ－１，３－ジメチルイミダゾリウムクロライド０．２５ｇ（１．４８ｍｍｏｌ）を加え、さらに氷冷下１時間、室温で１時間撹拌した。クロロホルムで希釈した後、水を加え、水層をクロロホルムで抽出した。

【０１８７】

有機層を飽和食塩水洗浄後、乾燥、溶媒を留去して得た残渣をシリカゲルカラムクロマトグラフィー（クロロホルム：メタノール＝１０：１）で精製し、得られた固体をエチルエーテルで洗浄することにより、Ｎ－（２－ｔｅｒｔ－ブトキシカルボニルアミノフェニル）－４－（Ｎ－ベンジルアミノ）カルボニルベンズアミド（２７９ｍｇ，６２．６％）を白色固体として得た。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.45(9H,s), 4.52(2H,d,J=5.8Hz), 7.13-7.28(4H,m), 7.34-7.35(3H,m), 7.56(2H,d,J=8.1Hz), 8.05(4H,s), 8.71(1H,br.s), 9.23(1H,t), 9.94(1H,s).

【０１８８】

（７７－６）　工程（７７－５）で得た化合物（１５１ｍｇ，０．３３９ｍｍｏｌ）に４規定塩酸－ジオキサン溶液（５ｍｌ）を室温で加え、４時間撹拌した。溶媒を留去した後、酢酸エチル／飽和重曹水で分離し、析出した沈澱を除いた後に水層をさらに酢酸エチルで抽出した。有機層を飽和食塩水で洗浄後、乾燥、溶媒を留去して得た残渣にエチルエーテルを加え、析出した沈澱を濾取、乾燥することによりＮ－（２－アミノフェニル）－４－（Ｎ－ベンジルアミノ）カルボニルベンズアミド（７８ｍｇ，６７％）を白色固体として得た。

mp. 239-241℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.51(2H,s), 4.93(2H,br.d), 6.60(1H,dd,J=7.3,7.3Hz), 6.78(1H,d,J=8.1Hz), 6.95(1H,dd,J=7.3,8.3Hz), 7.18(1H,d), 7.23-7.35(5H,m), 8.01, 8.07(4H,d,J=8.8Hz), 9.22(1H,br.t), 9.81(1H,br.s).

【０１８９】

実施例７７に記載と同様の方法により、実施例７８の化合物を合成した。以下に、化合物の融点（mp.）、1H NMR、IRの測定値を示す。

【０１９０】

実施例７８

Ｎ－（２－アミノフェニル）－４－［Ｎ－（２－フェニルエチル）アミノ］カルボニルベンズアミド（表－１：化合物番号９）

mp. 237-240℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 2.87(2H,t,7.3), 3.51(2H,dt,5.9,7.3), 4.94(2H,br.s), 6.60(1H,dd,7.3,7.3), 6.78(1H,d,7.3), 6.98(1H,dd,7.3,7.3), 7.15-7.34(6H,m), 7.93(2H,d,8.1), 8.04(2H,d,8.1), 8.73(1H,t,5.1), 9.76(1H,br.s).

IR(KBr)cm-1: 3396,3320,1625,1602,1539,1458,1313,699.

【０１９１】

実施例７９

Ｎ－（２－アミノフェニル）－４－［Ｎ－（４－ニトロフェノキシアセチル）アミノ］ベンズアミド（表－１：化合物番号１５８）の合成

（７９－１）　実施例６４の工程（６４－２）で得られた化合物３ｇ（９．２ｍｍｏｌ）、４－ニトロフェノキシ酢酸２．１６ｇ（１１．０ｍｍｏｌ）のＤＭＦ溶液（７ｍｌ）にジシクロヘキシルカルボジイミド２．８２ｇ（１３．８ｍｍｏｌ）のＤＭＦ溶液（５ｍｌ）、触媒量のＮ，Ｎ－ジメチルアミノピリジンを加え１日間撹拌した。反応終了後、酢酸エチルを加え、不溶物をセライト濾過し、溶媒を留去した。

【０１９２】

得られた残留物をクロロホルムから再結晶し、Ｎ－［２－（ｔｅｒｔ－ブトキシカルボニルアミノ）フェニル］－４－［（４－ニトロフェノキシアセチル）アミノ］ベンズアミド２．３４ｇを得た（収率５０％）。

1H NMR(270MHz, DMSO-d6) δ ppm: 1.45(9H,s),4.97(2H,s),7.12-7.26(3H,m),7.23(2H,d,J=8.80),7.53(1H,dt,J=2.20,7.35),7.79(2H,d,J=8.80),7.95(2H,d,J=8.80),8.25(2H,d,J=8.80),8.71(1H,s),9.79(1H,s),10.52(1H,s).

【０１９３】

（７９－２）　工程（７９－１）で得られた化合物０．７ｇ（１．３８ｍｍｏｌ）のアセトニトリル溶液（１０ｍｌ）に室温でヨードトリメチルシラン１．２６

ml（8．85mmol）を加え、2時間撹拌した。反応終了後、溶媒を濃縮し、酢酸エチルを加え20分間撹拌し、析出した結晶を濾取した。得られた結晶をメチルエチルケトンに溶解し、飽和チオ硫酸ナトリウム水溶液、飽和食塩水で順次洗浄し、無水硫酸マグネシウムで乾燥し、溶媒を留去した。得られた残留物を酢酸エチルで洗浄し、N－（2－アミノフェニル）－4－[N－（4－ニトロフェノキシアセチル）アミノ]ベンズアミド0．22gを白色結晶として得た（収率39％）。

mp. 212-215℃(dec.).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.97(2H,s),6.88(1H,t,J=7.35),6.99(1H,d,J=7.35),7.11(1H,t,J=7.35),7.23(2H,d,J=8.80),7.24(1H,1H,m),7.77(2H,d,J=8.80),8.00(2H,d,J=8.80),8.25(2H,d,J=8.80),9.89(1H,s),10.52(1H,s).

IR(KBr)cm-1: 3382,3109,1650,1591,1508,1341.

【0194】

実施例80

N－（2－アミノフェニル）－4－[（4－アミノフェノキシアセチル）アミノ]ベンズアミド（表－1：化合物番号159）の合成

実施例79の工程（79－1）で得られた化合物1．41g（2．78mmol）のメタノール（15ml）－THF（25ml）溶液に10％Pd－Cを加え水素雰囲気下室温で1時間撹拌した。反応終了後、触媒を濾過し溶媒を濃縮後、ジイソプロピルエーテルでスラッジングして、N－[2－（tert－ブトキシカルボニルアミノ）フェニル]－4－[（4－アミノフェノキシアセチル）アミノ]ベンズアミド1．1gを得た。

【0195】

これをアセトニトリル15mlに溶解し、ヨードトリメチルシラン0．74ml（5．20mmol）を加え、室温で3時間撹拌した。反応終了後、溶媒を濃縮しメチルエチルケトンで洗浄して、N－（2－アミノフェニル）－4－[（4－アミノフェノキシアセチル）アミノ]ベンズアミド0．86gを得た。（収率83％）

mp. (amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.82(2H,s),7.13(2H,d,J=8.80),7.30-7.48(6H,m),7.82(2H,d,J=8.80),8.03(2H,d,J=8.80),10.34(1H,s),10.46(1H,s).

IR(KBr)cm-1: 2873,2590,1680,1602,1505,1243.

【0196】

薬理試験例1

A2780細胞に対する分化誘導作用試験

アルカリフォスファターゼ（ALP）活性の上昇は、ヒト大腸癌細胞の分化の指標として知られており、例えば酪酸ナトリウムがALP活性を上昇させることが知られている［Youngら；Cancer Res.、45、2976（1985）、Moritaら；Cancer Res.、42、4540（1982）］。そこでALP活性を指標に分化誘導作用の評価を行った。

【0197】

（実験方法） 96穴プレートに15,000ヶ／well となるように、A2780細胞を0．1ml ずつまき、翌日培地にて段階希釈した被験薬の溶液を0．1ml ずつ添加した。3日間培養後、プレート上の細胞をTBS緩衝液（20mM Tris，137mM NaCl、pH7．6）で2回洗浄した。ついで、0．6mg／ml の濃度のp－ニトロフェニルフォスフェイト（9．6% ジエタノールアミン、0．5mM $MgCl_2$（pH9．6））溶液を0．05ml ずつ添加し、室温で30分インキュベートした。3規定NaOH溶液0．05ml で反応を停止した後、405nmの吸光度を測定し、ALP活性の上昇を惹起する薬物の最小濃度（ALPmin）を求めた。

（実験結果） 実験結果を、表－2［表17］に示した。

【0198】

【表17】

表－2：A2780細胞に対する分化誘導作用

供試化合物	ALPmin（μM）
実施例4の化合物	1
実施例5の化合物	1

実施例８の化合物	1
実施例９の化合物	1
実施例１０の化合物	3
実施例１１の化合物	1
実施例１３の化合物	1
実施例１５の化合物	3
実施例１６の化合物	3
実施例１８の化合物	3
実施例２３の化合物	1
実施例２４の化合物	1
実施例２５の化合物	3
実施例２６の化合物	1
実施例２７の化合物	10
実施例２８の化合物	10
実施例２９の化合物	10
実施例３０の化合物	0.1
実施例３１の化合物	0.1
実施例３２の化合物	0.1
実施例３３の化合物	1
実施例３４の化合物	1
実施例３５の化合物	1
実施例３６の化合物	3
実施例３７の化合物	3
実施例３８の化合物	1
実施例３９の化合物	1
実施例４０の化合物	3
実施例４１の化合物	3
実施例４２の化合物	3
実施例４３の化合物	3

実施例４４の化合物	3
実施例４７の化合物	3
実施例４８の化合物	3
実施例４９の化合物	3
実施例５０の化合物	3
実施例５１の化合物	3
実施例５２の化合物	3
実施例５３の化合物	30
実施例５４の化合物	0.1
実施例５５の化合物	0.3
実施例５６の化合物	3
実施例５７の化合物	0.1
実施例５８の化合物	3
実施例５９の化合物	3
実施例６０の化合物	10
実施例６１の化合物	0.1
実施例６２の化合物	0.1
実施例６３の化合物	3
実施例６４の化合物	1
実施例６６の化合物	3
実施例６８の化合物	1
実施例７０の化合物	1
実施例７１の化合物	1
実施例７２の化合物	3
実施例７３の化合物	1
実施例７４の化合物	3
実施例７５の化合物	3
実施例７６の化合物	0.1

【０１９９】

薬理試験例２

抗腫瘍作用試験

（実験方法）　ヌードマウス皮下で継代された腫瘍細胞（ＨＴ－２９，ＫＢ－３－１）をヌードマウスに移植し、体積が２０－１００ｍｍ^{3}程度になり、生着が確認されたところで薬剤の投与を開始した。これを１日目とし以後１－５日、８－１２日、１５－１９日および２２－２６日に薬剤を経口投与した。

腫瘍体積は、（腫瘍体積）＝１／２ｘ（長径）ｘ（短径）^{2} により求めた。

【０２００】

（実験結果）　ＨＴ－２９に対する実施例３２の化合物（投与量６６μｍｏｌ／ｋｇ）の実験結果を、［図１］に示した。

【０２０１】

ＫＢ－３－１に対する実施例３２の化合物（投与量６６μｍｏｌ／ｋｇ）の実験結果を、［図２］に示した。

【０２０２】

【発明の効果】本発明の新規ベンズアミド誘導体は分化誘導作用を有し、医薬品として有用である。特に、制癌剤として効果が高く、造血器腫瘍、固形癌に有効である。

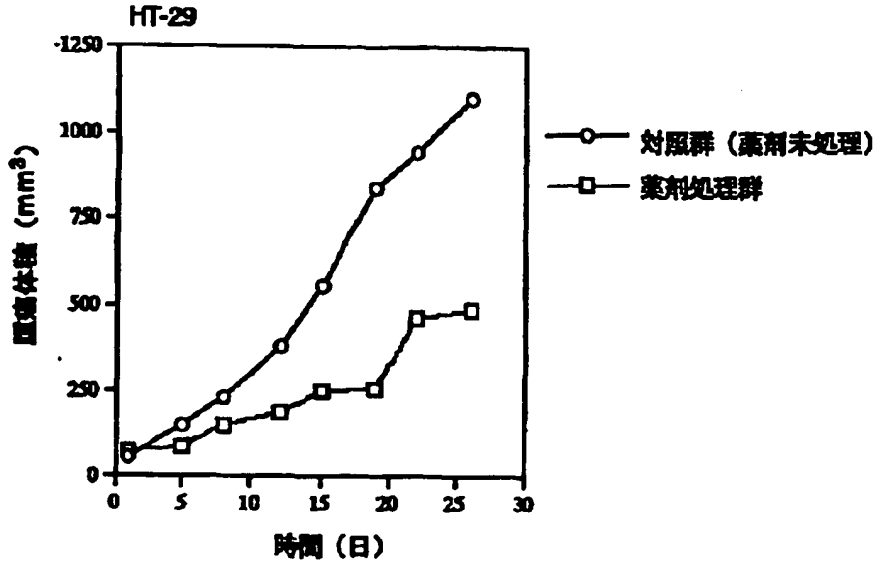
【図面の簡単な説明】

【図１】：ＨＴ－２９に対して実施例３２の化合物投与時の腫瘍体積の変化を示す図である。

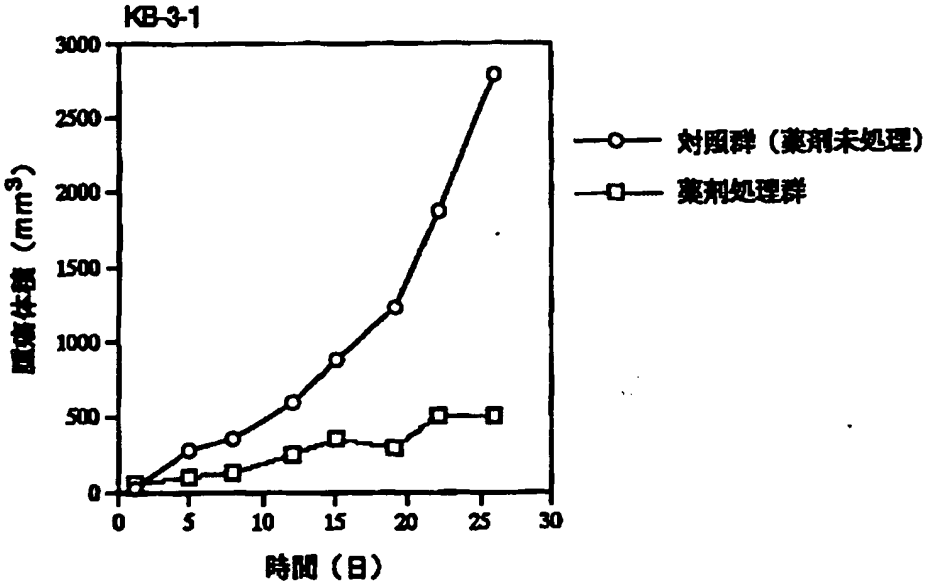
【図２】：ＫＢ－３－１に対して実施例３２の化合物投与時の腫瘍体積の変化を示す図である。

【書類名】 図面

【図１】


HT-29
腫瘍体積 (mm³)
1250
1000
750
500
250
0
0
5
10
15
20
25
30
時間（日）
対照群（薬剤未処理）
薬剤処理群

【図２】

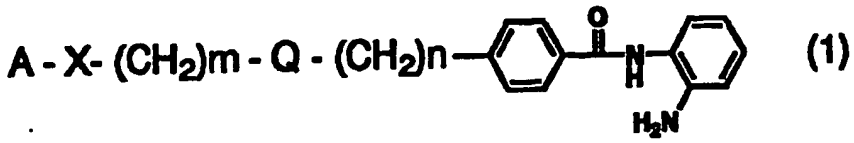

KB-3-1
腫瘍体積 (mm³)
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
時間（日）
対照群（薬剤未処理）
薬剤処理群

【書類名】要約書

【要約】

【課題】　分化誘導作用を有する新規ベンズアミド誘導体を提供すること。

【解決手段】　一般式（１）で示される新規ベンズアミド誘導体。



(1)

【効果】　一般式（１）で示される本発明の新規ベンズアミド誘導体は分化誘導作用を有するため、悪性腫瘍、自己免疫疾患、皮膚病の治療・改善剤として有用である。特に、制癌剤として効果が高く、造血器腫瘍、固形癌に有効である。

【選択図】なし

【書類名】　職権訂正データ
【訂正書類】　特許願

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Japanese Application of

Tsuneji SUZUKI, et al.

Japanese Patent Application No.: 258863/1996

Japanese Patent Filing Date: September 30, 1996

for: "Cell Differentiation Inducer"

VERIFICATION OF TRANSLATION

Honorable Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

Jun NAKAGAWA residing at 3-7-21, Shibayama, Funabashi-shi, Chiba, Japan, declares:

(1) that he knows well both the Japanese and English languages;

(2) that he translated the above-identified Japanese Application from Japanese to English;

(3) that the attached English translation is a true and correct translation of the above-identified Japanese Application to the best of his knowledge and belief; and

(4) that all statements made of his own knowledge are true and that all statements made on information and belief and believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 USC 1001, and that such false statements may jeopardize the validity of the application or any patent issuing thereof.

December 3, 2002

Date

Jun Nakagawa

Jun NAKAGAWA

PATENT OFFICE

JAPANESE GOVERNMENT

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Applicant(s): MITSUI TOATSU CHEMICALS, INC.

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Commissioner, Toshimitsu ARAI (seal)

Patent Office

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[Title of the Invention] Novel Benzamide derivatives

[Number of Claims] 6

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[Indication of Official Fees]

[Advance Deposit Record Number] 010021

[Amount paid] 21000

[List of Materials Submitted]

[Material Name]	Specification	1
[Material Name]	Drawings	1
[Material Name]	Abstract	1

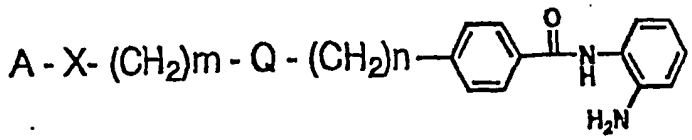
[Proof] Not Requested

[Document Name] Specification

[Title of the Invention] Novel Benzamide derivatives

[Claims]

[Claim 1] A benzamide derivative represented by the general formula (1):



(1)

[wherein A is an optionally substituted phenyl or an optionally substituted heterocyclic group which have 1 to 4 groups as a substituent(s) selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X represents a direct bond, $-O-$, $-S-$ or $-NH-$;

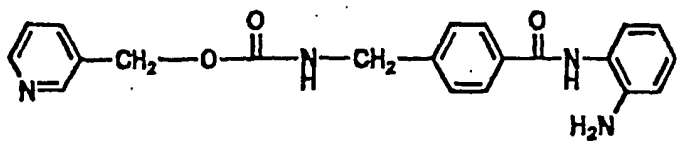
n and m are independently an integer of 0 to 4, provided that there is no case that both n and m are zero;

Q represents any one of an amido bond, a thioamido bond, an urethane bond, a thiourethane bond, an urea bond or a thiourea bond]

or a pharmaceutically acceptable salt thereof.

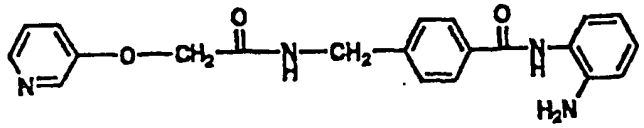
[Claim 2] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in Claim 1, wherein A is an optionally substituted pyridyl group.

[Claim 3] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in Claim 1, which is represented by the formula (2):



(2)

[Claim 4] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in Claim 1, which is represented by the formula (3):



(3)

[Claim 5] An anticancer agent comprising at least one of the compounds described in any one of Claims 1 to 4 as an active ingredient.

[Claim 6] A medical and pharmaceutical product comprising at least one of the compounds described in any one of Claims 1 to 4 as an active ingredient.

[Detailed Explanation of the Invention]

[0001]

[Industrial Field of the Invention]

This invention relates to a novel benzamide derivative. Further in detail, this invention relates to an anticancer agent based on the differentiation-inducing effect of the novel benzamide derivative and its uses for other medical and pharmaceutical products.

[0002]

[Prior Art]

Cancers have now become a top cause of death, exceeding heart and cerebrovascular diseases, and so many studies have been conducted with enormous expense and time to overcome cancers. They have not been, however, overcome in spite of a variety of investigations for therapy such as a surgical operation, a radiation therapy and thermotherapy. Among those therapies, chemotherapy is one of the main areas for cancer treatment. To date, however, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity and high therapeutic effect has been desired. Many of the conventional anticancer drugs show their effect by affecting mainly DNA to express their cytotoxicity and then injuring carcinoma cells. However, since they do not have sufficient selectivity between carcinoma cells and normal cells, adverse reactions expressed in normal cells have limited their use in therapy.

[0003]

Meanwhile, differentiation-inducing agents among anticancer drugs are aimed to induce differentiation of carcinoma cells for controlling their infinite proliferation, rather than directly kill the cells. The agents may, therefore, be inferior to the anticancer drugs directly killing carcinoma cells, with regard to involution of a carcinoma, but may be expected to have reduced toxicity and different selectivity. In fact, it is well known that retinoic acid, a differentiation-inducing agent, is used for treatment of acute promyelogenous leukemia, and is potent [Huang et al., Blood, 72, 567-572(1988); Castaign et al., Blood, 76, 1704-1709 (1990); Warrell et al., New Engl. J. Med. 324, 1385-1393(1991) etc.]. In addition, vitamin D derivatives exhibit differentiation-inducing effect, and thus their application for anticancer drugs have been investigated [e.g., Olsson et al, Cancer Res. 43, 5862-5867(1983) etc.].

[0004]

As the results of these investigations, there have been reported applications of a variety of differentiation-inducing agents such as vitamin D derivatives (JP-A 6-179622), isoprene derivatives (JP-A 6-192073), tocopherol (JP-A 6-256181), quinone derivatives (JP-A 6-305955), noncyclic polyisoprenoids (JP-A 6-316520), benzoic acid derivatives (JP-A 7-206765) and glycolipids (JP-A 7-258100), for anticancer drugs. There have been no agents having sufficient level of effect for cancer treatment in spite of the investigations, and thus there has been greatly desired a highly safe agent effective to a variety of cancers.

[0005]

[Problems to be solved by the Invention]

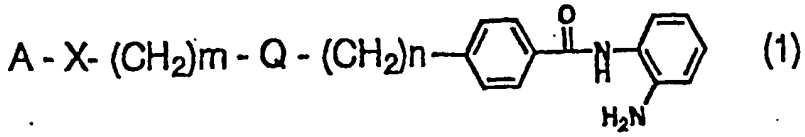
The object of the present invention is to provide compounds which exhibit differentiation-inducing effects and are useful as medical and pharmaceutical agents such as therapeutic or improving agents for malignant tumors, autoimmune diseases and dermatologic diseases.

[0006]

The present inventors intensely researched in order to achieve the object and have found that a novel benzamide derivative having differentiation-inducing effect show antitumor effect. As a result, this invention has been completed. Specifically, the present invention is:

[1] A benzamide derivative represented by the general formula (1):

[0007]



(1)

[wherein A is an optionally substituted phenyl or an optionally substituted heterocyclic group which have 1 to 4 groups as a substituent(s) selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;

X represents a direct bond, $-O-$, $-S-$ or $-NH-$;

n and m are independently an integer of 0 to 4, provided that there is no case that both n and m are zero;

Q represents any one of an amido bond, a thioamido bond, an urethane bond, a thiourethane bond, an urea bond or a thiourea bond]

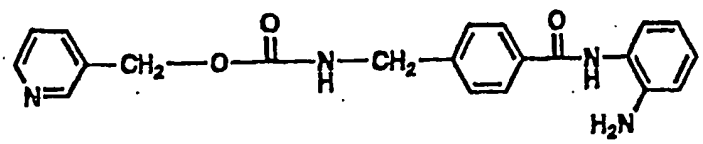
or a pharmaceutically acceptable salt thereof;

[0008]

[2] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in [1], wherein A is an optionally substituted pyridyl group;

[3] A benzamide derivative or a pharmaceutically acceptable salt thereof as claimed in [1], which is represented by the formula (2);

[0009]

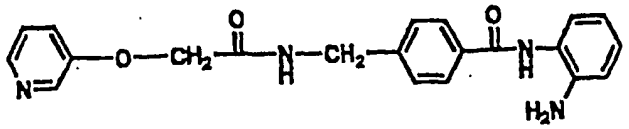


(2)

[4] A benzamide derivative or a pharmaceutically acceptable salt thereof as

claimed in [1], which is represented by the formula (3);

[0010]



(3)

[0011]

[5] An anticancer agent comprising at least one of the compounds described in any one of [1] to [4] as an active ingredient; and

[0012]

[6] A medical and pharmaceutical product comprising at least one of the compounds described in any one of [1] o [4] as an active ingredient.

[0013]

[Embodiments for carrying out the Invention]

The present invention is explained in detail below.

In the present invention, "1 to 4 carbons" means a carbon number per a single substituent; for example, for dialkyl substitution, it means 2 to 8 carbons.

A heterocycle in the compound represented by the general formula (1) may be a 5 or 6-membered ring containing 1 to 4 nitrogen, oxygen or sulfur atoms. Their examples include pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isoxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinuclidine, tetrahydrofuran, morpholine, thiomorpholine and the like.

[0014]

A halogen atom may be fluorine, chlorine, bromine or iodine atom.

An alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

[0015]

An alkoxy having 1 to 4 carbons includes methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

An aminoalkyl having 1 to 4 carbons includes aminomethyl, 1-aminoethyl, 2-aminopropyl and the like.

[0016]

An alkylamino having 1 to 4 carbons includes N-methylamino, N,N-dimethylamino, N,N-diethylamino, N-methyl-N-ethylamino, N,N-diisopropylamino and the like.

An acyl having 1 to 4 carbons includes acetyl, propanoyl, butanoyl and like.

[0017]

An acylamino having 1 to 4 carbons includes acetylamino, propanoylamino, butanoylamino and the like.

An alkylthio having 1 to 4 carbons includes methylthio, ethylthio, propylthio and the like.

A perfluoroalkyl having 1 to 4 carbons includes trifluoromethyl, pentafluoroethyl and the like.

[0018]

A perfluoroalkyloxy having 1 to 4 carbons includes trifluoromethoxy, pentafluoroethoxy and the like.

An alkoxycarbonyl having 1 to 4 carbons includes methoxycarbonyl and ethoxycarbonyl.

A pharmaceutically acceptable salt of the compound of this invention includes salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; and with an organic acid such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and the like, which are used generally in this field.

As used herein, a "medical and pharmaceutical product" in claim 6 includes a therapeutic and/or improving agent, for example, an anticancer drug, a drug against an autoimmune disease or dermatologic disease.

When it has an asymmetric carbon or carbons at "A" in the general formula (1), it may be present as an individual stereoisomer or a mixture of the stereoisomers including a racemic modification. This invention encompasses the above defined various forms, which may be also used as an active ingredient.

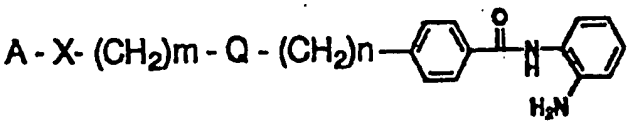
[0019]

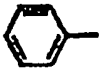
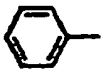
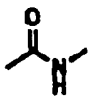
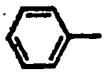
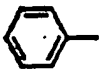
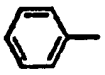
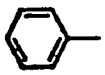
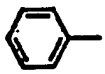
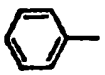
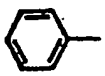
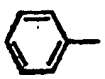
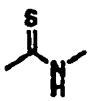
Representative compounds of this invention represented by the general formula (1) are specifically shown in Table 1, but this invention is not

intended to be limited to these.

[0020]

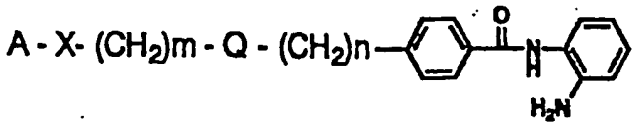
Table 1

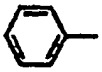
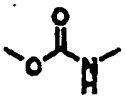
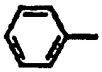
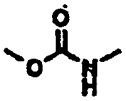
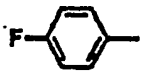
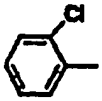
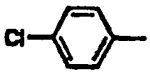
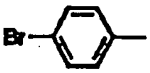
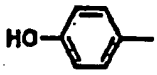
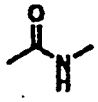
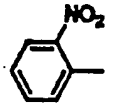
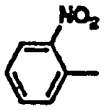
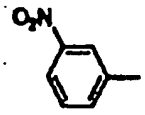
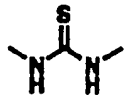


Compound No.	A	X	m	Q	n
1		Direct Bond	0		1
2		Direct Bond	1		0
3		Direct Bond	2		0
4		Direct Bond	3		0
5		Direct Bond	4		0
6		Direct Bond	1		1
7		Direct Bond	2		1
8		Direct Bond	1		0
9		Direct Bond	2		0
10		Direct Bond	0		1

[0021]

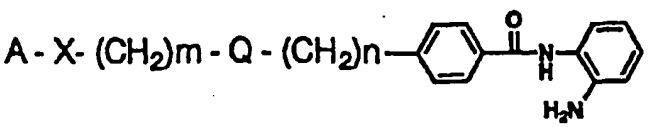
Table 1 (Cont.1)

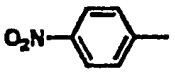
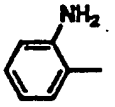
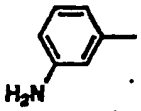
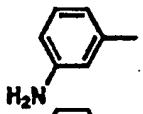
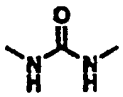
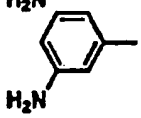
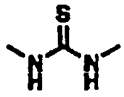
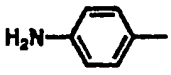
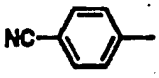
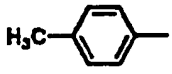
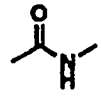
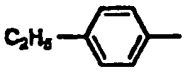
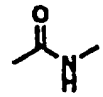
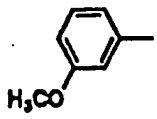
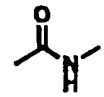


Compound No.	A	X	m	Q	n
11		Direct Bond	1		1
12		Direct Bond	0		1
13		Direct Bond	0		1
14		Direct Bond	0		1
15		Direct Bond	1		0
16		Direct Bond	0		1
17		Direct Bond	0		1
18		Direct Bond	0		1
19		Direct Bond	1		0
20		Direct Bond	0		1

[0022]

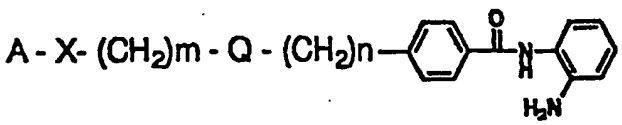
Table 1 (Cont. No. 2)

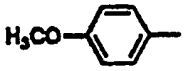
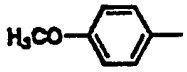
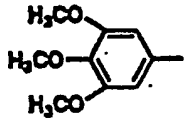
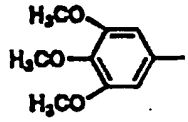
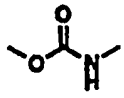
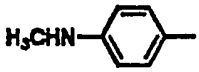
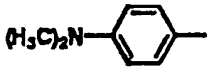
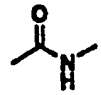
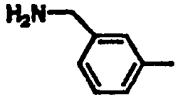
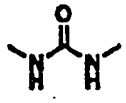
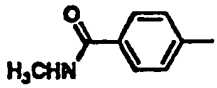
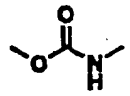
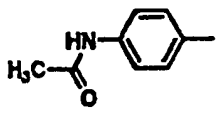
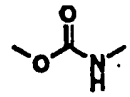
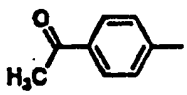


Compound No.	A	X	m	Q	n
2 1		Direct Bond	1		0
2 2		Direct Bond	1		0
2 3		Direct Bond	1		1
2 4		Direct Bond	0		1
2 5		Direct Bond	0		1
2 6		Direct Bond	1		0
2 7		Direct Bond	0		1
2 8		Direct Bond	0		1
2 9		Direct Bond	0		1
3 0		Direct Bond	0		1

[0023]

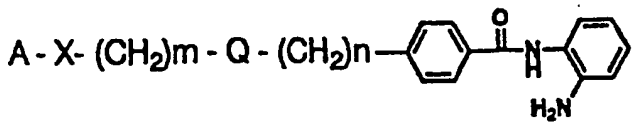
Table 1 (Cont. No. 3)

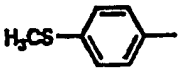
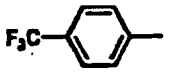
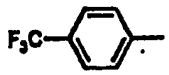
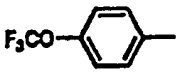
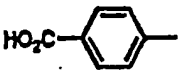
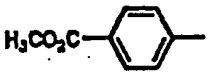
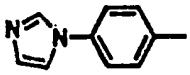
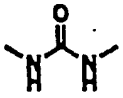
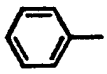
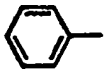
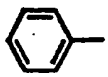


Compound No.	A	X	m	Q	n
3 1		Direct Bond	0		1
3 2		Direct Bond	1		0
3 3		Direct Bond	0		1
3 4		Direct Bond	1		1
3 5		Direct Bond	0		1
3 6		Direct Bond	0		1
3 7		Direct Bond	0		1
3 8		Direct Bond	1		1
3 9		Direct Bond	1		1
4 0		Direct Bond	0		1

[0024]

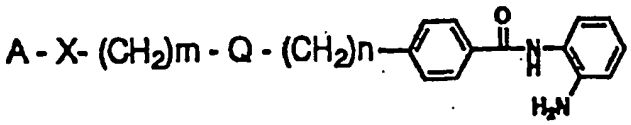
Table 1 (Cont. No. 4)

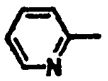
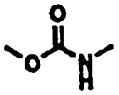
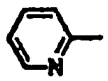
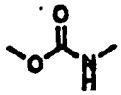
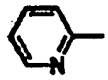
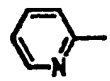
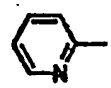
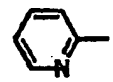
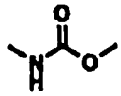
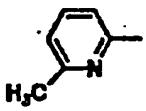
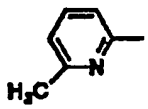
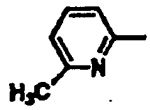
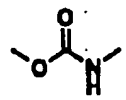
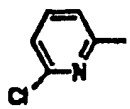
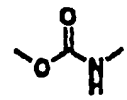


Compound No.	A	X	m	Q	n
41		Direct Bond	0		1
42		Direct Bond	0		1
43		Direct Bond	1		0
44		Direct Bond	0		1
45		Direct Bond	0		1
46		Direct Bond	0		1
47		Direct Bond	1		1
48		—O—	1		1
49		—S—	1		1
50		—N—	1		1

[0025]

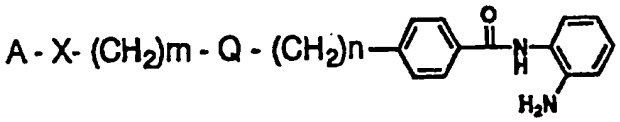
Table 1 (Cont. No. 5)

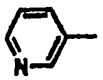
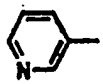
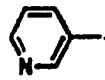
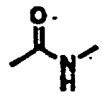
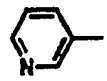
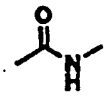
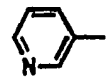
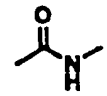
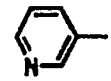
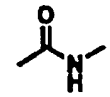
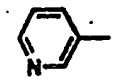
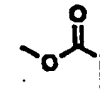
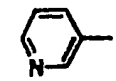
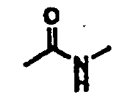
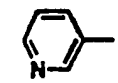
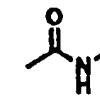
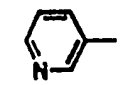


Compound No.	A	X	m	Q	n
5 1		Direct Bond	1		1
5 2		Direct Bond	2		1
5 3		Direct Bond	0		1
5 4		Direct Bond	1		0
5 5		Direct Bond	1		0
5 6		Direct Bond	1		1
5 7		Direct Bond	1		0
5 8		Direct Bond	0		1
5 9		Direct Bond	1		1
6 0		Direct Bond	1		1

[0026]

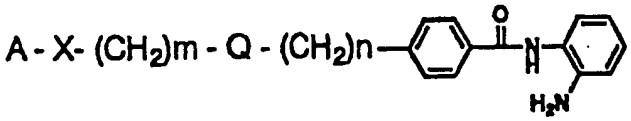
Table 1 (Cont. No. 6)

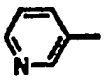
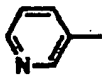
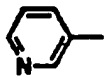
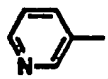
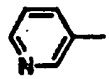
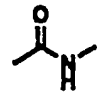
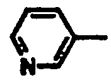
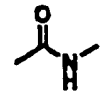
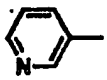
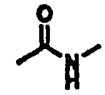
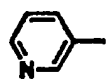
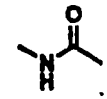
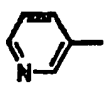
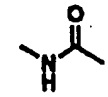
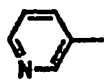
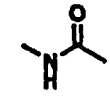


Compound No.	A	X	m	Q	n
61		—O—	1		1
62		—O—	2		1
63		—N—	1		1
64		—S—	1		1
65		—O—	1		0
66		—O—	2		0
67		—O—	2		0
68		Direct Bond	1		0
69		Direct Bond	2		0
70		Direct Bond	3		0

[0027]

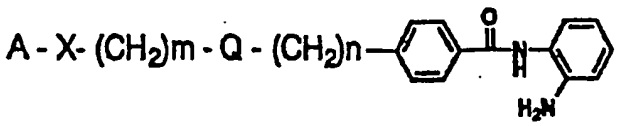
Table 1 (Cont. No. 7)

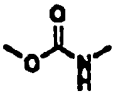
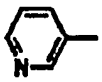
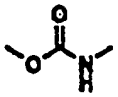
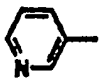
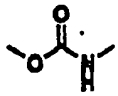
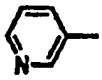
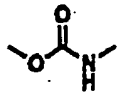
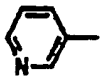
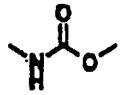
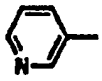
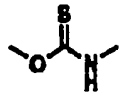
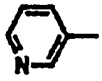
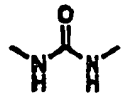
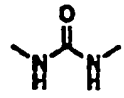
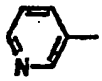
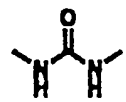
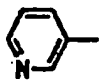
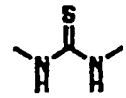


Compound No.	A	X	m	Q	n
7 1		Direct Bond	0		1
7 2		Direct Bond	0		2
7 3		Direct Bond	0		3
7 4		Direct Bond	1		1
7 5		Direct Bond	2		1
7 6		Direct Bond	3		1
7 7		Direct Bond	1		2
7 8		Direct Bond	1		1
7 9		Direct Bond	0		2
8 0		Direct Bond	1		2

[0028]

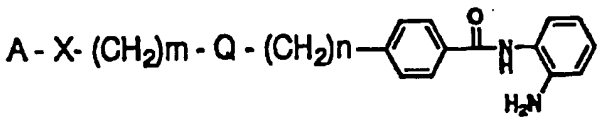
Table 1 (Cont. No. 8)

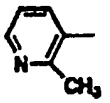
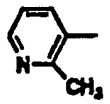
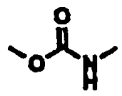
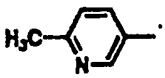
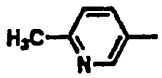
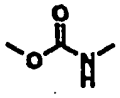
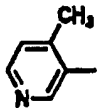
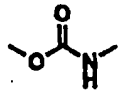
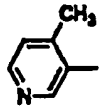
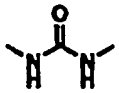
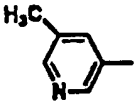
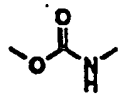
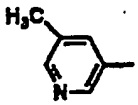
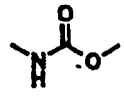
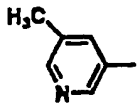
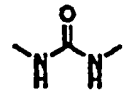
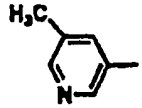


Compound No.	A	X	m	Q	n
8 1		Direct Bond	0		1
8 2		Direct Bond	1		1
8 3		Direct Bond	2		1
8 4		Direct Bond	3		1
8 5		Direct Bond	1		1
8 6		Direct Bond	1		1
8 7		Direct Bond	0		1
8 8		Direct Bond	1		1
8 9		Direct Bond	2		1
9 0		Direct Bond	1		1

[0029]

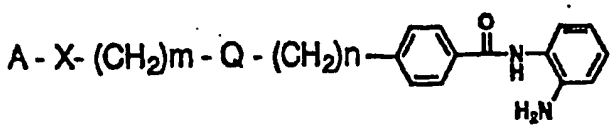
Table 1 (Cont. No. 9)

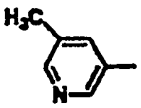
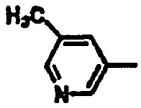
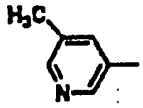
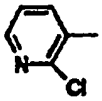
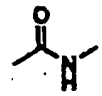
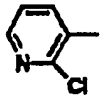
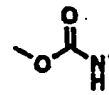
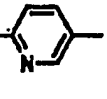
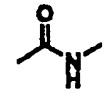
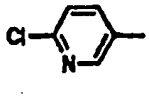
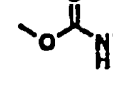
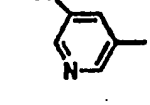
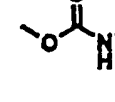
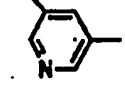
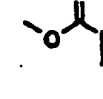


Compound No.	A	X	m	Q	n
9 1		Direct Bond	0		1
9 2		Direct Bond	1		1
9 3		Direct Bond	0		1
9 4		Direct Bond	1		1
9 5		Direct Bond	1		1
9 6		Direct Bond	1		1
9 7		Direct Bond	1		1
9 8		Direct Bond	1		1
9 9		Direct Bond	1		1
1 0 0		Direct Bond	2		1

[0030]

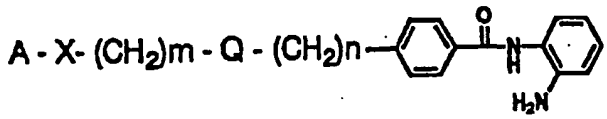
Table 1 (Cont. No. 10)

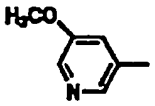
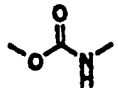
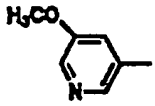
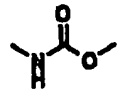
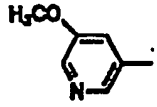
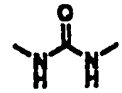
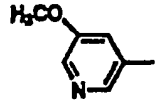
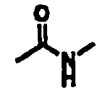
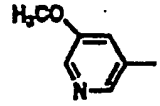
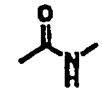
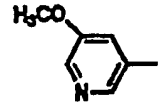
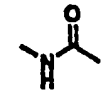
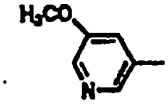
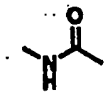
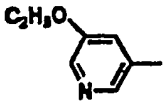
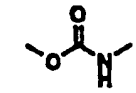
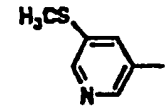
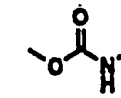
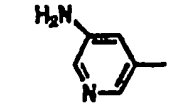
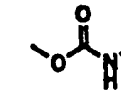


Compound No.	A	X	m	Q	n
101		Direct Bond	2		1
102		Direct Bond	2		0
103		Direct Bond	1		2
104		Direct Bond	0		1
105		Direct Bond	1		1
106		Direct Bond	0		1
107		Direct Bond	1		1
108		Direct Bond	1		1
109		Direct Bond	1		1
110		Direct Bond	1		1

[0031]

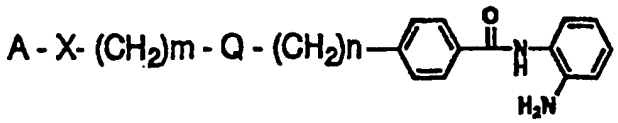
Table 1 (Cont. No. 11)

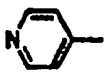
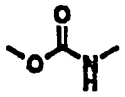
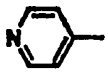
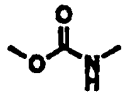
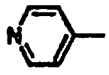
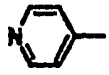
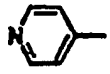
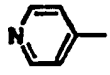
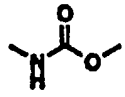
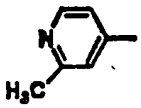
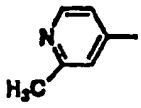
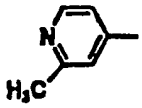
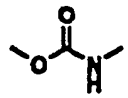
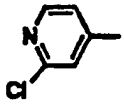
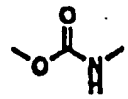


Compound No.	A	X	m	Q	n
111		Direct Bond	1		1
112		Direct Bond	1		1
113		Direct Bond	1		1
114		Direct Bond	2		1
115		Direct Bond	2		1
116		Direct Bond	2		0
117		Direct Bond	1		2
118		Direct Bond	1		1
119		Direct Bond	1		1
120		Direct Bond	1		1

[0032]

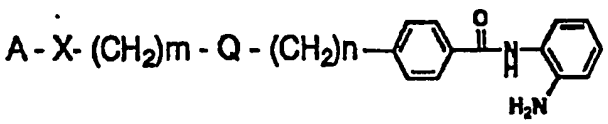
Table 1 (Cont. No. 12)

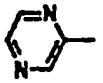
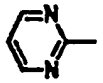
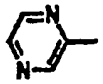
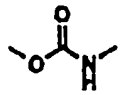
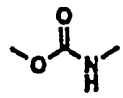
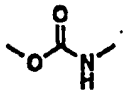
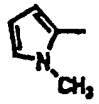
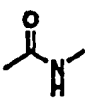


Compound No.	A	X	m	Q	n
121		Direct Bond	1		1
122		Direct Bond	2		1
123		Direct Bond	0		1
124		Direct Bond	1		0
125		Direct Bond	1		0
126		Direct Bond	1		1
127		Direct Bond	1		0
128		Direct Bond	0		1
129		Direct Bond	1		1
130		Direct Bond	1		1

[0033]

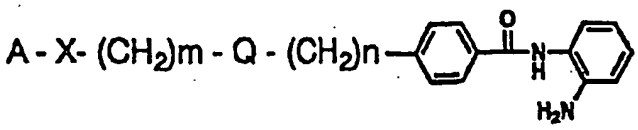
Table 1 (Cont. No. 13)

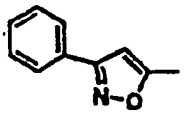
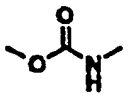
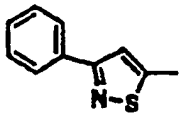
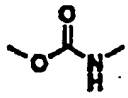
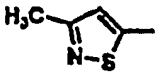
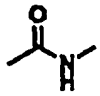
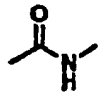
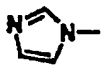
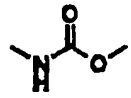
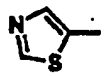
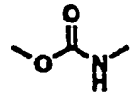
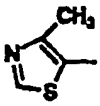
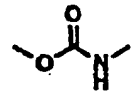
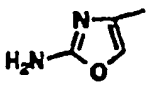
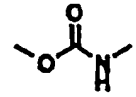
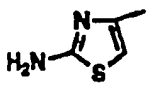
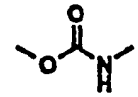


Compound No.	A	X	m	Q	n
131		Direct Bond	0		1
132		Direct Bond	0		1
133		Direct Bond	0		1
134		Direct Bond	0		1
135		Direct Bond	1		1
136		Direct Bond	2		1
137		Direct Bond	0		1
138		Direct Bond	1		1
139		Direct Bond	0		1
140		Direct Bond	0		1

[0034]

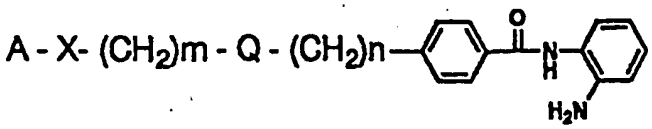
Table 1 (Cont. No. 14)

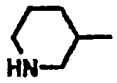
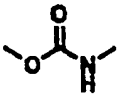
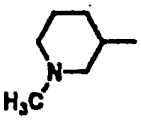
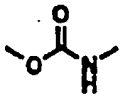
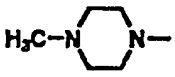
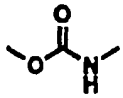
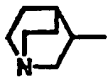
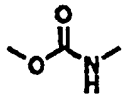
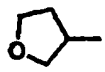
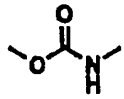
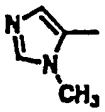
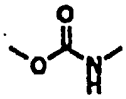
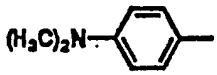
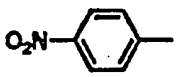
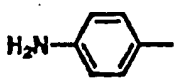
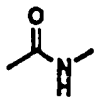


Compound No.	A	X	m	Q	n
141		Direct Bond	1		1
142		Direct Bond	1		1
143		Direct Bond	0		1
144		Direct Bond	0		1
145		Direct Bond	0		1
146		Direct Bond	3		1
147		Direct Bond	1		1
148		Direct Bond	2		1
149		Direct Bond	1		1
150		Direct Bond	1		1

[0035]

Table 1 (Cont. No. 15)



Compound No.	A	X	m	Q	n
151		Direct Bond	1		1
152		Direct Bond	1		1
153		Direct Bond	3		1
154		Direct Bond	1		1
155		Direct Bond	1		1
156		Direct Bond	1		1
157		Direct Bond	1		0
158		—O—	1		0
159		—O—	1		0

[0036]

The compound of this invention may be prepared, for example, as described below.

(a) A compound represented by the general formula (4);

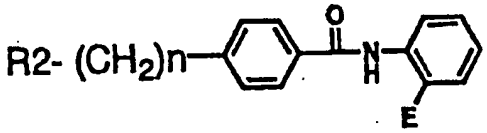
[0037]

$$A\text{-}X\text{-}(CH_2)m\text{-}R1 \qquad (4)$$

wherein A, X and m are as defined above; R1 is -C(=G)OH (G is an oxygen or sulfur atom) or $-NH_2$;

is condensed with a compound represented by the general formula (5);

[0038]



(5)

wherein n is as defined as above; R2 is $-NH_2$ when R1 is -C(=G)OH (G is an oxygen or sulfur atom) and -C(=G)OH (G is an oxygen or sulfur atom) when R1 is $-NH_2$; E is an amino group bound with a protective group used in a common peptide-forming reaction, e.g., tert-butoxycarbonyl.

Alternatively,

(b) a compound represented by the general formula (6)

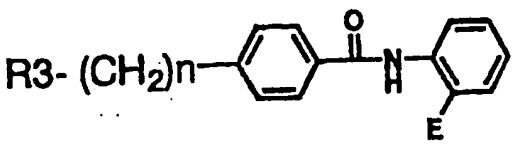
[0039]

$$A\text{-}X\text{-}(CH_2)m\text{-}R3$$

wherein A, X and m are as defined above; and R3 is -OH or $-NH_2$;

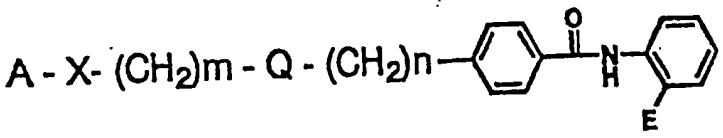
is condensed with a compound represented by the general formula (7);

[0040]



(7)

wherein R3, n and E are as defined above;
by using an agent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, phosgene or thiophosgene, to give a compound represented by the general formula (8):
[0041]

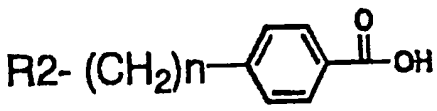


(8)

wherein A, X, m, Q, n and E are as defined above;
and the protecting group is then removed from it to give the desired compound.

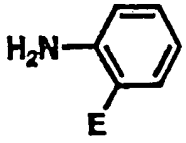
The compound represented by the general formula (4) is commercially available or may be produced by the method in the example described later.

The compound of the general formula (5) may be obtained by introducing a suitable protecting group into a benzoic acid derivative represented by the general formula (9):
[0042]



(9)

wherein R2 and n are defined as above;
subjecting the resulting product to condensation with a compound represented by the general formula (10):
[0043]



(10)

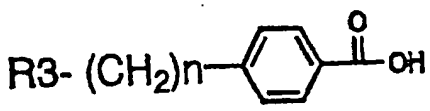
wherein E is defined as above;
and leaving the protecting group.

[0044]

The compound of the general formula (6) is commercially available or may be produced by the method in the example described later.

The compound represented by the general formula (7) can be obtained by introducing a suitable protecting group in to a benzoic acid derivative represented by the general formula (11):

[0045]



(11)

wherein R3 and n are defined as above;
subjecting the resulting product to condensation with a compound represented by the general formula (10) and leaving the protecting group.

The compound represented by the general formula (11) is commercially available or may be produced by the method in the example described later.

[0046]

The condensation reaction in (a) may be an amido-bond forming reaction for a usual peptide using, for example, an activated ester, a mixed acid anhydride or an acid chloride. For example, a carboxylic acid, i.e., a compound represented by the general formula (4) wherein R1 is $-C(=G)OH$ (G is an oxygen or sulfur atom) or a compound represented by the general formula (5) wherein R2 is $-C(=G)OH$ (G is an oxygen or sulfur atom), may be condensed with a phenol derivative such as 2,4,5-trichlorophenol, pentachlorophenol or 4-nitrophenol, or an N-hydroxy compound such as N-hydoxysuccinimide or N-hydroxybenzotriazole, in the presence of dicyclohexylcarbodiimide, to be converted into an activated ester, which is then condensed with an amine represented by the general formula (4) wherein R1 is $-NH_2$ or by the general formula (5) wherein R2 is $-NH_2$, to give the desired product.

[0047]

Alternatively, a carboxylic acid represented by the general formula (4) wherein R1 is $-C(=G)OH$ (G is an oxygen or sulfur atom) or by the general formula (5) wherein R2 is $-C(=G)OH$ (G is an oxygen or sulfur atom), may be reacted with, for example, oxalyl chloride, thionyl chloride or phosphorus oxychloride to be converted into an acid chloride, which is then condensed with an amine represented by the general formula (4) wherein R1 is $-NH_2$ or by the general formula (5) wherein R2 is $-NH_2$, to give the desired product.

[0048]

Furthermore, a carboxylic acid represented by the general formula (4) wherein R1 is $-C(=G)OH$ (G is an oxygen or sulfur atom) or by the general formula (5) wherein R2 is $-C(=G)OH$ (G is an oxygen or sulfur atom), may be reacted with, for example, isobutyl chlorocarbonate or methanesulfonyl chloride to be converted into a mixed acid anhydride, which is then condensed with an amine represented by the general formula (4) wherein R1 is $-NH_2$ or by the general formula (5) wherein R2 is $\cdot NH_2$, to give the desired product.

The above condensation reaction may be conducted solely using a peptide condensing agent such as dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, diphenyl phosphoric azide, diethylphosphorylcyanide, etc.

[0049]

The reaction may be usually conducted at -20 to $+50$ ℃ for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; N,N-dimethylformamide; alcohols such as methanol, ethanol and the like; and a mixture thereof. If necessary, an organic base such as triethylamine or pyridine may be added.

[0050]

The condensation reaction in (b) may be conducted by activating a compound represented by either the general formula (6) or (7) with, for example, phosgene, thiophosgene, N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole or the like and then reacting the activated product with the other compound. The reaction may be usually conducted at

−20 to +50 ℃ for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; N,N-dimethylformamide; and a mixture thereof. If necessary, an organic base such as triethylamine, pyridine and the like may be added.

[0051]

Removal of the protecting group in the compound represented by the general formula (8) is carried out under the condition used in the general reaction for peptide production. For example, when E in the general formula (8) is the amino group protected with tert-butoxycarbonyl, the removal reaction of the protecting group can be carried out by treatment with an acid such as hydrochloric acid or the like.

[0052]

A salt of a compound represented by the general formula (1) may be formed during preparation of the compound of the general formula (1), but is usually formed with a pharmaceutically acceptable acid. Such an acid includes inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; and organic acids such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and the like. These salts may be also used as an active ingredient in this invention, as the free form of the compound represented by the general formula (1).

[0053]

A compound represented by the general formula (1) may be purified or isolated by a usual separation method such as extraction, recrystallization, column chromatography and the like.

[0054]

The novel benzamide derivative of this invention has differentiation-inducing effect and thus is useful as a therapeutical and improving agent to a variety of diseases such as malignant tumors, autoimmune diseases and dermatologic diseases.

As used herein, a "malignant tumor" includes hematologic malignancy such as acute leukemia, chronic leukemia, malignant lymphoma, multiple

myeloma or macroglobulinemia as well as solid tumors such as colon cancer, cerebral tumor, head and neck tumor, breast carcinoma, pulmonary cancer, esophageal cancer, gastric cancer, hepatic cancer, gallbladder cancer, bile duct cancer, pancreatic cancer, nesidioblastoma, renal cell carcinoma, adrenocortical cancer, urinary bladder carcinoma, prostatic cancer, testicular tumor, ovarian carcinoma, uterine cancer, chorionic carcinoma, thyroid cancer, malignant carcinoid tumor, skin cancer, malignant melanoma, osteogenic sarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumor and retinoblastoma.

An autoimmune disease shows rheumatism, nephritis and diabetes.

The dermatologic diseases include psoriasis, acne, exanthema and atopic dermatitis.

The diseases to be targeted by the present invention are not limited to these specific examples.

[0055]

The active ingredient compounds of this invention are useful as a drug, which may be used in the form of a general pharmaceutical composition. The pharmaceutical composition may be prepared with generally used diluents or excipients such as filler, extender, binder, moisturizing agent, disintegrator, surfactant and lubricant. The dosage form of the pharmaceutical composition may be selected from a variety of dosage forms depending on its therapeutic purpose; typically tablet, pill, powder, solution, suspension, emulsion, granule, capsule, injection (e.g., solution, suspension) and suppository.

[0056]

For preparing tablets, a variety of carriers well-known in the art may be widely used. Such a carrier includes excipients such as lactose, sucrose, sodium chloride, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate and polyvinyl pyrrolidone;

[0057]

disintegrators such as dried starch, sodium alginate, powdered agar, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid

esters, sodium lauryl sulfate, stearic acid monoglyceride, starch and lactose; disintegration retarders such as sucrose, stearic acid, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch; adsorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates, bronic acid powder and polyethylène glycol. The tablet may be, if necessary, one coated with a common coating; for example, sugar-coated tablet, gelatin-coated tablet, enteric coated tablet, film-coated tablet, and the tablet may be a double-layer tablet or multilayer tablet.

[0058]

In forming pills, a variety of carriers well-known in the art may be widely used. Such a carrier includes excipients such as glucose, lactose, starch, cacao-oil, hydrogenated vegetable oil, kaoline and talc; binders such as powdered acacia gum, powdered tragacanth gum and gelatin; disintegrators such as calcium carmelose and agar.

Capsule may be prepared by blending an active ingredient with a variety of the above carriers as usual and filling the resulting blend into, for example, a hard gelatin or soft capsule or the like.

[0059]

For preparing injection, solution, emulsion and suspension are sterilized and preferably isotonic with blood. It may be prepared using diluents commonly used in the art; for example, water, ethanol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. The pharmaceutical preparation may contain sodium chloride, glucose or glycerin necessary to prepare an isotonic solution, as well as usual solubilizers, buffers and soothing agents may be added.

[0060]

Suppository may be formed by widely using a variety of well-known carriers; for example, polyethylene glycol, cacao oil, higher alcohols, higher alcohol esters, gelatin and semi-synthetic glyceride.

Furthermore, the pharmaceutical composition may contain coloring agents, preservatives, perfumes, flavors, sweeteners or other drugs.

The amount of the active ingredient in the pharmaceutical composition of this invention may be, as appropriate, selected from a wide range with no limitations, and is generally about 1 to 70 % by weight in the composition, preferably about 5 to 50 % by weight.

[0061]

An administration route of the pharmaceutical composition is not limited, and selected depending on its composition form, patient's age, sex, severity of disease and other conditions. For example, tablet, pill, solution, suspension, emulsion, granule and capsule may be orally administered; injection may be intravenously administered solely or in combination with a common infusion fluid such as glucose, amino acids and the like, or if necessary, intramuscularly, subcutaneously or intraperitoneally as a sole preparation. Suppository may be intrarectally administered.

[0062]

Dose of the pharmaceutical preparation of this invention may be selected, depending on their dosage form, patient's age, sex and severity of disease, and other conditions, as appropriate, but the amount of the active ingredient may be generally about 0.0001 to 100 mg/kg a day. It is recommended that a unit dosage form may contain about 0.001 to 1000 mg of the active ingredient.

The compound represented by the general formula (1) of this invention or a salt thereof exhibits no toxicity at the dose showing pharmacological effects.

[0063]

[Examples]

This invention will be specifically illustrated with, but is not limited to, the following examples. The numbers in parentheses indicate those of the compounds are those shown in the above detailed description.

Example 1

Preparation of N-(2-aminophenyl)-4-(N-benzoylaminomethyl) benzamide hydrochloride (Table 1: hydrochloride of Compound 1):

[0064]

(1-1) To a suspension of 4-aminomethylbenzoic acid(21.16 g, 140 mmol) in dichloromethane (450 ml) was added triethylamine (42 ml, 300 mmol).

Under ice-cooling, trifluoroacetic anhydride (60.4 g, 287 mmol) in dichloromethane (50 ml) were added dropwise, maintaining the inner temperature at 3 to 8 ℃, and then the mixture was stirred four 3 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution, and was acidified with 10 % hydrochloric acid. The gel precipitate was collected by filtration and dried to give 4-(N-trifluoroacetylaminomethyl) benzoic acid (30.4 g, Yield: 87.8 %) as an opalescent solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 4.47(2H, d, 5.8), 7.39(2H, d, 8.1), 7.93(2H, d, 8.1), 10.08(1H, t, 5.8), 12.95(1H, br.s.)

[0065]

(1-2) To a solution of o-phenylenediamine (54.0 g, 500 mmol) in dioxane (500 ml) was added 1N sodium hydroxide aq.(250 ml), and then di-tert-butoxy dicarbonate (109.1 g, 550mmol) in dioxane (250 ml) under ice-cooling. After stirring for 6 hours at room temperature, the mixture was left overnight. The mixture was concentrated to 1/2 volume by evaporation, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography (eluent: chloroform) to give a solid, which was then washed with diethyl ether to give N-tert-butoxycarbonyl-o-phenylenediamine (34.2 g, Yield: 32.8 %) as a white solid.

1H NMR (270 MHz, CDCl3) δ ppm: 1.51(9H, s), 3.75(2H, s), 6.26(1H, s), 6.77(1H, d, J=8.1 Hz), 6.79(1H, dd, J=7.3, 8.1 Hz), 7.00(1H, dd, J=7.3, 8.1 Hz), 7.27(1H, d, J=8.1 Hz)

[0066]

(1-3) To a suspension of the compound from the process (1-1) (30 g, 121 mmol) in dichloromethane (200 ml) were slowly added dropwise oxalyl chloride (21 g, 165 mmol) with intermittently adding DMF (0.1 ml per 2 ml addition), maintaining the inner temperature within 10 to 15 ℃ by ice-cooling. After completion of the addition, the mixture was stirred until bubble generation ceased, and then at 40 ℃ for an additional hour. After evaporation, excess oxalyl chloride was azeotropically removed with toluene, and then the residue was redissolved in dichloromethane (100 ml). The prepared acid chloride solution was added dropwise to a solution of the compound from the process (1-2) (22.88 g, 110 mmol) in dichloromethane (100

ml) and pyridine (200 ml), maintaining the inner temperature within 7 to 9 ℃ by ice-cooling.

[0067]

After addition, the mixture was warmed to room temperature, and was left overnight. After adding saturated sodium bicarbonate aq. to the reaction mixture, the resulting mixture was extracted with chloroform, and the organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give N-[2-(N-tert-butoxycarbonyl) aminophenyl]-4-trifluoroacetylaminomethylbenzamide (28.1 g, Yield: 58 %) as a light yellow solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 1.44(9H, s), 4.48(2H, d, 5.9), 7.12-7.23(2H, m), 7.44(2H, d, 8.1), 7.54(2H, d, 8.1), 7.94(2H, d, 8.1), 8.68(1H, br.s), 9.83(1H, s), 10.10(1H, br.t, 5.9)

[0068]

(1-4) To a suspension of the compound from the process (1-3) (13.12 g, 30 mmol) in methanol (120 ml) and water (180 ml) were added potassium carbonate (4.70 g, 34.0 mmol), and the mixture was heated with stirring at 70 ℃ for 4 hours. It was extracted with chloroform, and the organic layer was washed with saturated brine, dried, evaporated and dried to give 4-aminomethyl-N-[2-(N-tert-butoxycarbonyl)aminophenyl]benzamide (10.3 g, Yield: quantitative) as a light yellow amorphous solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 3.80(2H, s), 7.13-7.23(2H, m), 7.48-7.58(4H, m), 7.90(2H, d, 8.1), 8.69(1H, br.s), 9.77(1H, br.s)

[0069]

(1-5) To a solution of the compound from the process (1-4) (0.11 g, 0.44 mmol) in pyridine (5 ml) was added benzoyl chloride (0.08 g, 0.53 mmol) under ice-cooling, and the mixture was gradually warmed to room temperature and then stirred for 8 hours. Saturated sodium bicarbonate aq. was added, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether, and the solid obtained was dried to give N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(N-benzoylaminomethyl)benzam ide (0.14 g, Yield: 71.4 %) as a white solid.

1H NMR (270 MHz, DMSO-d6) δ ppm: 1.44(9H, s), 4.56(2H, d, 5.9), 7.11-7.22(2H, m), 7.46-7.56(7H, m), 7.90-7.94(4H,m), 8.67(1H, s), 9.15(1H, t, 5.9), 9.81(1H, s)

[0070]

(1-6) To a solution of the compound from the process (1-5) (0.10 g, 0.224 mmol) in dioxane (5 ml) and methanol (1 ml) was added 4N hydrochloric acid-dioxane (5 ml), and the mixture was stirred at room temperature for 7 hours. To the residue after evaporation was added diisopropyl ether, and the formed solid was collected by filtration and dried to give N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (0.08 g, Yield: 93 %) as a light brown solid.

mp: 206-209 ℃

1H NMR (270 MHz, DMSO-d6) δ ppm: 4.57(2H, d, 5.8), 7.27-7.38(4H, m), 7.47-7.59(5H, m), 7.92(1H, d, 8.1), 8.05(1H, d, 8.1), 9.19(1H, t, 5.8), 10.38(1H, br.s)

IR(KBr, cm-1): 3286, 3003(br.), 1630, 1551, 1492, 1306, 1250, 749, 695.

As described in Example 1, the compounds of Examples 2 to 30 were prepared, each of whose melting point (mp), 1H NMR data, IR data are described below.

[0071]

Example 2

N-(2-aminophenyl)-4-[N-(2-chlorobenzoyl)aminomethyl]benzamide (Table 1: Compound 14)

mp: 201-204 ℃(dec.).

1H NMR (270MHz, DMSO-d6) δ ppm: 4.52(2H, t, 5.9), 4.89(2H, br.s), 6.60(1H, ddd, 1.5, 7.3, 8.1), 6.78(1H, dd, 1.5, 8.1), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.17(1H, d, 8.1), 7.38-7.54(6H,m), 7.97(2H, d, 8.1), 9.06(1H, br.t, 5.9), 9.63(1H, br.s)

IR (KBr) cm-1: 3268, 1649, 1458, 1304, 748

[0072]

Example 3

N-(2-aminophenyl)-4-[N-(2-nitrobenzoyl)aminomethyl]benzamide hydrochloride(Table 1: hydrochloride of Compound 18)

mp: 210-212 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm : 4.55(2H, t, 5.9), 7.20-7.40(3H, m),

7.50-7.6(1H, m), 7.53(2H, d, 8.1), 7.60-7.70(2H, m), 7.83(1H, ddd, 1.5, 8.1, 8.1), 8.00-8.10(3H, m), 9.34(1H, t, 5.9), 10.43(1H, br.s)

IR(KBr)cm-1 :3283, 2500-3000(br.), 1648, 1534, 1461, 1362, 1314, 754, 701

[0073]

Example 4

N-(2-aminophenyl)-4-[N-(4-methylbenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 28)

mp:(amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm : 2.37(3H, s), 4.56(2H, d, 5.0), 7.20-7.30(6H, m), 7.47(4H, d, 8.8), 7.82(2H, d, 8.8), 8.03(2H, d, 8.8), 9.09(1H, t, 5), 10.36(1H, br.s)

IR(KBr)cm-1:3269(br.), 2861(br.), 1743, 1636, 1534, 1505, 1456, 1308, 1120, 753.

[0074]

Example 5

N-(2-aminophenyl)-4-[N-(3-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 30)

mp: 182-185 ℃

1H NMR(270MHz, DMSO-d6) δ ppm: 3.81(3H, s), 4.54(2H,d, 5.9), 4.88(2H, br.s) , 6.60(1H, dd, 6.6, 7.3), 6.78(1H, d, 7.3), 6.97(1H, dd, 6.6, 7.3), 7.11(1H, dd, 1.5, 8.1), 7.16(1H, d, 7.3), 7.35-7.51(5H, m), 7.94(2H, d, 8.1), 9.12(1H, br.t, 5.9), 9.63(1H, br.s)

IR(KBr)cm-1: 3301, 1637, 1524, 1489, 1457, 1314, 1248, 752

[0075]

Example 6

N-(2-aminophenyl)-4-[N-(4-methoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 31)

mp: 149-151 ℃

1H NMR(270MHz, DMSO-d6) δ ppm: 3.82(3H, s), 4.53(2H, d, 5.9), 4.88(2H, s), 6.59(1H, dd, 7.3, 7.3), 6.77(1H, d, 8.1), 6.94-7.00(1H,m), 7.02(2H, d, 8.8), 7.16(1H, d, 8.1), 7.43(2H, d, 8.1), 7.89(2H, d, 8.8), 7.94(2H, d, 8.1), 8.98(1H, br.t, 5.9), 9.61(1H, br.s)

IR(KBr)cm-1: 3297, 1630, 1527, 1505, 1457, 1256, 1177, 1024, 843, 749

[0076]

Example 7

N-(2-aminophenyl)-4-[N-(3,4,5-trimethoxybenzoyl)aminomethyl]benzamide (Table 1: Compound 33)

mp: 208-210 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 3.71(3H, s), 3.83(6H, s), 4.55(2H, d, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, dd, 6.6, 8.1), 7.16(1H, d, 8.1), 7.26(2H, s), 7.44(2H, d, 8.1), 7.95(2H, d, 8.8), 9.07(1H, t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3267, 1635, 1582, 1457, 1237, 1132, 755

[0077]

Example 8

N-(2-aminophenyl)-4-[N-[4-(N,N-dimethyl)aminobenzoyl]aminomethyl]benzamide (Table 1: Compound 36)

mp: 216-219 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 2.98(6H, s), 4.51(2H, d, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 8.1, 8.1), 6.71(2H, d, 8.8), 6.97(1H, ddd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.41(2H, d, 8.1), 7.78(2H, d, 8.8), 7.93(2H, d, 8.1), 8.77(1H, t, 5.9), 9.63(1H, br.s).

IR(KBr)cm-1: 3301, 1632, 1519, 1457, 1298, 754

[0078]

Example 9

N-(2-aminophenyl)-4-[N-(4-trifluoromethylbenzoyl)aminomethyl]benzamide (Table 1: Compound 42)

mp: 243-246 ℃.

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H, d, 5.9), 4.88(2H,br.s), 6.59(1H,dd, 6.6, 7.3), 6.77(1H, d, 8.1), 6.94(1H, dd, 5.9, 6.6), 7.16(1H, d, 8.1), 7.45(2H, d, 8.1), 7.88(2H, d, 8.8), 7.95(2H, d, 8.1), 8.11(2H, d, 8.1), 9.38(1H, t, 5.9), 9.64(1H, br.s)

IR(KBr)cm-1: 3301, 1640, 1549, 1523, 1458, 1334, 1162, 1120, 1070, 856, 750

[0079]

Example 10

N-(2-aminophenyl)-4-[N-(4-carboxybenzoyl)aminomethyl]benzamide hydrochloride (Table 1: hydrochloride of Compound 45)

mp: (amorphous).

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H, d, 5.9), 7.29-7.37(3H, m), 7.49(3H, d, 8.1), 8.02-8.06(6H, m), 9.36(1H, t, 5.9), 10.4(1H, br.s)
IR(KBr)cm-1: 3432(br.), 1718, 1637, 1542, 1499, 1303(br.), 1116, 1018, 757
[0080]
Example 11
N-(2-aminophenyl)-4-[N-(4-methoxycarbonylbenzoyl)aminomethyl]benzamide (Table 1: Compound 46)
mp: 204-209 ℃(dec.)
1H NMR(270MHz, DMSO-d6) δ ppm: 3.89(3H, s), 4.57(2H, d, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 6.6, 7.3), 6.78(2H,d, 7.3), 6.97(1H, ddd, 1.5, 6.6, 7.3), 7.16(1H, d, 7.3), 7.45(2H, d, 8.1), 7.95(2H, d, 8.1), 8.03(2H, d, 8.8), 8.07(2H, d, 8.8), 9.35(1H, t, 5.9), 9.64(1H, br.s)
IR(KBr)cm-1: 3287(br.), 1721, 1634, 1281, 1113, 750, 703
[0081]
Example 12
N-(2-aminophenyl)-4-(N-picolinoylaminomethyl)benzamide (Table 1: Compound 53)
mp: 173-178 ℃(dec.)
1H NMR(270MHz, DMSO-d6) δ ppm: 4.57(2H, d, 6.6), 4.88(2H,br.s), 6.59(1H, dd, 7.3, 8.1), 6.77(1H, d, 8.1), 6.96(1H, dd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.44(2H, d, 8.1), 7.60-7.65(1H, m), 7.93(2H, d, 8.1), 7.98-8.08(2H, m), 8.67(1H, d, 4.4), 9.45(1H, t, 6.6), 9.61(1H, br s)
IR(KBr)cm-1: 3330, 1656, 1634, 1523, 1456, 1294, 752
[0082]
Example 13
N-(2-aminophenyl)-4-[N-(6-methylpicolinoyl)aminomethyl]benzamide (Table 1: Compound 58)
mp: 172-173 ℃
1H NMR(270MHz, DMSO-d6) δ ppm: 2.51(3H, s), 4.57(2H,d, 6.6), 5.0(2H, br.s), 6.61(1H, dd, 7.3, 8.1), 6.79(1H, d, 7.3), 6.98(1H, dd, 7.3, 8.1), 7.17(1H, d, 7.3), 7.44(2H, d, 8.1), 7.43-7.49(1H, m), 7.84-7.90(2H, m), 7.94(2H, d, 8.1), 9.27(1H, t, 5.9), 9.64(1H, br.s)
IR(KBr)cm-1: 3331, 1675, 1634, 1594, 1523, 1454, 1307, 1292, 750
[0083]

Example 14

N-(2-aminophenyl)-4-(N-nicotinoylaminomethyl)benzamide (Table 1: Compound 71)

mp: 193-196 ℃

1H NMR(270MHz, DMSO-d6) δ ppm: 4.58(2H, d), 4.88(2H, br.s), 6.60(1H, t), 6.78(1H, d), 6.97(1H, t), 7.16(1H, d), 7.46(2H, d), 7.53(1H, dd), 7.95(2H, d), 8.24(1H,ddd), 8.73(1H,dd), 9.07(1H,d), 9.32(1H,br.t), 9.63(1H, br.s)

IR(KBr)cm-1: 3301, 1639, 1522, 1457, 1314, 749, 705

[0084]

Example 15

N-(2-aminophenyl)-4-[N-(2-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 91)

mp: 191-194 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 2.53(3H, s), 4.53(2H,d, 5.9), 4.88(2H,br.s), 6.60(1H, dd, 6.6, 8.1), 6.78(1H, d, 7.3), 6.97(1H, dd, 7.3, 8.1), 7.17(1H, d, 7.3), 7.29(1H, dd, 5.1, 8.1), 7.47(2H, d, 8.1), 7.77(1H, dd, 1.5, 8.1), 7.97(2H, d, 8.1), 8.51(1H, dd, 1.5, 5.1), 9.06(1H, t, 5.9), 9.64(1H, s)

IR(KBr)cm-1: 3261, 1642, 1523, 1310, 753

[0085]

Example 16

N-(2-aminophenyl)-4-[N-(6-methylnicotinoyl)aminomethyl]benzamide (Table 1: Compound 93)

mp: 186-190 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.36(3H, s), 4.56(2H, d, 5.9), 4.88(2H, s), 6.60(1H, dd, 7.4, 7.8), 6.78(1H, d, 7.8), 6.97(1H, dd, 6.9, 6.9), 7.16(1H, d, 7.4), 7.37(1H, d, 8.3), 7.45(2H, d, 8.3), 7.95(2H, d, 8.3), 8.13(1H, dd, 2.0, 8.3), 8.96(1H, s), 9.24(1H, t, 5.9), 9.63(1H, br.s)

IR(KBr)cm-1: 3302, 1636, 1602, 1523, 1489, 1457, 1313, 751

[0086]

Example 17

N-(2-aminophenyl)-4-[N-(2-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 105)

mp: 176-178 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.54(2H, t, 5.9), 4.90(2H, br.s), 6.60(1H,

ddd, 1.5, 7.3, 7.3), 6.78(1H, d, 8.1), 6.97(1H, ddd, 1.5, 7.3, 7.3), 7.18(1H, d, 8.1), 7.48-7.54(3H, m), 7.94-7.99(3H, m), 8.49(1H, dd, 2.1, 5.1), 9.23(1H, br.t, 5.9), 9.65(1H, br.s)

IR(KBr)cm-1: 3264, 1649, 1524, 1400, 1309, 751

[0087]

Example 18

N-(2-aminophenyl)-4-[N-(6-chloronicotinoyl)aminomethyl]benzamide (Table 1: Compound 107)

mp: 205-208 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 5.57(2H, d, 5.9), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 8.1), 6.96(1H, dd, 7.3, 8.1), 7.16(1H, d, 8.1), 7.45(2H, d, 8.1), 7.66(1H, d, 8.8), 7.95(2H, d, 8.1), 8.27-32(1H, m), 8.90(1H, d, 2.1), 9.38(1H, t, 5.9), 9.63(1H, s)

IR(KBr)cm-1: 3318(br.), 2929, 1646, 1590, 1525, 1503, 1454, 1108, 745

[0088]

Example 19

N-(2-aminophenyl)-4-(N-isonicotinoylaminomethyl)benzamide (Table 1: Compound 123)

mp: 234-237 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.57(2H, t, 5.9), 4.88(2H,br.s), 6.59(1H,dd, 6.6, 7.3), 6.78(1H, d, 8.1), 6.96(1H, dd, 7.3, 7.3), 7.16(1H, d, 7.3), 7.45(2H, d, 8.1), 7.81(2H, d, 1.5, 4.4), 7.95(2H, d, 8.1), 8.75(2H, d, 6.6), 9.41(1H, t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3298, 1646, 1550, 1525, 1457, 1304, 843, 760, 695

[0089]

Example 20

N-(2-aminophenyl)-4-[N-(pyrazin-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 131)

mp: 207 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.58(2H, d, 5.9), 4.88(2H,br.s), 6.59(1H,dd, 7.3, 7.3), 6.77(1H, d, 8.1), 6.94(1H, ddd, 1.5, 7.3, 8.1), 7.15(1H, d, 7.3), 7.45(2H, d, 8.1), 7.93(2H, d, 8.1), 8.77(1H, d, 1.5), 8.90(1H, d, 2.1), 9.21(1H, s), 9.55-9.61(2H, m)

IR(KBr)cm-1: 3368(br.), 1657, 1524, 1455, 1295, 1023, 751

[0090]

Example 21

N-(2-aminophenyl)-4-[N-(thiophen-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 134)

mp: 202-205 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.52(2H, t, 5.9), 4.88(2H, br.s), 6.60(1H, dd, 6.6, 7.3), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.15-7.18(2H, m), 7.43(2H,d, 8.1), 7.78(1H, d, 4.4), 7.82(1H, d, 3.7), 7.95(2H, d, 8.1), 9.12(1H, br.t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3306, 1633, 1523, 1456, 1297, 750, 716

[0091]

Example 22

N-(2-aminophenyl)-4-(N-furoylaminomethyl)benzamide (Table 1: Compound 137)

mp: 197 ℃(dec.)

1H NMR(270MHz. DMSO-d6) δ ppm: 4.59(2H, d, 6.6), 4.86(2H,br.s), 6.59(1H, t, 6.6), 6.63(1H, dd, 1.5, 3.6), 6.78(1H, d, 8.1), 6.96(1H, dd, 7.3, 6.6), 7.10-7.20(2H, m), 7.41(2H, d, 8.1), 7.84(1H, s), 7.94(2H, d, 8.1), 9.00(1H, br.t, 5.9), 9.62(1H, s)

IR(KBr)cm-1: 3245, 1651, 1573, 1545, 1323, 1241, 745

[0092]

Example 23

N-(2-aminophenyl)-4-[N-(pyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 139)

mp: 216-220 ℃(dec.)

1H NMR(270MHz, DMSO-d6) δ ppm: 4.50(2H, d, 5.9), 4.88(2H,br.s), 6.10(1H,dd, 2.1, 5.9), 6.59(1H, dd, 7.3, 7.3), 6.77(1H, dd, 1.5, 8.1), 6.84-6.88(2H, m), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 7.3), 7.41(2H, d, 8.1), 7.94(2H, d, 8.1), 8.62(1H, br.t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3275, 1655, 1584, 1534, 1458, 1316, 747

[0093]

Example 24

N-(2-aminophenyl)-4-[N-(N'-methylpyrrol-2-yl)carbonylaminomethyl]benzamide (Table 1: Compound 140)

mp: 177-179 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(3H, s), 4.46(2H, d, 5.9), 4.88(2H, d, 5.9), 6.03(1H, dd, 2.1, 4.4), 6.59(1H, dd, 8.1, 8.1), 6.77(1H, d, 8.1), 6.84-6.97(2H, m), 7.16(1H, d, 7.3), 7.41(2H, d, 8.1), 7.93(2H, d, 8.1), 8.61(1H, t, 5.9), 9.62(1H, br.s)

IR(KBr)cm-1: 3325(br.), 1630, 1551, 1520, 1507, 1324, 1265, 1154, 740

[0094]

Example 25

N-(2-aminophenyl)-4-[N-(isoxazol-5-carbonyl)aminomethyl]benzamide (Table 1: Compound 143)

mp: 183-185 ℃(dec.)

1H NMR(270 MHz. DMSO-d6) δ ppm: 4.53(2H, d, 6.6), 4.89(2H, br.s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 7.3), 6.97(1H, dd, 7.3, 8.1), 7.12(1H, d, 2.1), 7.16(1H, d, 8.1), 7.44(2H, d, 8.1), 7.95(2H, d, 8.1), 8.76(1H, d, 1.5), 9.61(1H, t, 5.9), 9.64(1H, br.s)

IR(KBr)cm-1: 3278(br.), 1636, 1576, 1522, 1458, 1220, 749

[0095]

Example 26

N-(2-aminophenyl)-4-[N-(3-methylisothiazol-5-carbonyl)aminomethyl] benzamide (Table 1: Compound 144)

mp: 168-169 ℃.

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.47(3H, s), 4.54(2H, d, 5.9), 4.89(2H, br.s), 6.60(1H,dd, 7.3, 7.3), 6.78(1H, d, 7.3), 6.97(1H, ddd, 1.0, 7.3, 8.1), 7.17(1H, d, 7.3), 7.44(2H, d, 8.1), 7.73(1H, s), 7.96(2H, d, 8.1), 9.44(1H, t, 5.9), 9.64(1H, br.s)

IR(KBr)cm-1: 3310, 1637, 1503, 1294, 751

[0096]

Example 27

N-(2-aminophenyl)-4-[N-(imidazol-4-carbonyl)aminomethyl]benzamid e (Table 1: Compound 145)

mp: (amorphous).

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.49(2H, d, 6.4), 4.87(2H, br.s), 6.59(1H, dd, 6.9, 6.9), 6.77(1H, d, 6.9), 6.96(1H, dd, 7.4, 7.4), 7.16(1H, d, 6.9), 7.41(2H,d, 6.9), 7.64(1H, br. s), 7.73(1H, br.s), 7.92(2H, d, 6.9), 8.56(1H, br.t, 6.4), 9.61(1H,

s), 12.5(1H, br.s)

IR(KBr)cm-1: 3278(br.), 1636, 1576, 1522, 1458, 1220,749

[0097]

Example 28

N-(2-aminophenyl)-4-[N-(3-aminophenyl)acetylaminomethyl]benzamide (Table 1: Compound 23)

mp: 171-176 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.34(2H, d, J=5.9 Hz), 5.24(4H, br.s), 6.48-6.63(4H, m), 6.78-6.81(1H, m), 6.94-7.00(2H, m), 7.18(1H, d, J=8.1 Hz), 7.34(2H, d, J=8.1 Hz), 7.92(2H, d, J=8.1 Hz), 8.50(1H, t, J=5.9 Hz), 9.61(1H, s)

[0098]

Example 29

N-(2-aminophenyl)-4-[N-(pyridin-3-yl)acetylaminomethyl]benzamide (Table 1: Compound 74)

mp: 127 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(2H, s), 4.40(2H, d, J=5.88), 7.15-7.29(3H, m), 7.37(1H, d, J=6.62), 7.43(2H, d, J=8.80), 7.96(1H, m), 7.98(2H, d, J=8.80), 8.40(1H, d, J=8.80), 8.79-8.87(3H, m), 10.20(1H, s)

[0099]

Example 30

N-(2-aminophenyl)-4-[3-(pyridin-3-yl)propionamido]benzamide (Table 1: Compound 75)

mp: 183-186 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.51(2H, t, 7.3), 2.88(2H, d, 7.3), 4.31(2H, d, 5.9), 4.89(2H, br.s), 6.60(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 8.1), 7.23(2H, d, 8.8), 7.28-7.33(1H, m), 7.63(1H, d, 8.1), 7.89(2H, d, 8.1), 8.41-8.45(3H, m), 9.62(1H, br.s)

IR(KBr)cm-1: 3407, 3313, 1640, 1552, 1522, 1456, 1309, 746, 717

[0100]

Example 31

Preparation of N-(2-aminophenyl)-4-[N-(pyridin-3-yl)oxyacetyl aminomethyl]benzamide (Table 1: Compound 61)

(31-1) To a suspension of 0.22 g of sodium hydride (5.5 mmol) in DMF (2 ml) was added dropwise a solution of 0.48 g of 3-hydroxypyridine (5.0mmol)

in DMF (2 ml) at room temperature, and the mixture was stirred for an hour. The resulting brown solution was ice-cooled, 0.81 ml of tert-butyl bromoacetate (5.5 mmol) was added, and the mixture was stirred under ice-cooling for an hour followed by stirring at room temperature for 2 hours. After addition of water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform: ethyl acetate = 5:1), to give 0.34 g of tert-butyl 3-pyridyloxyacetate (Yield: 32.5 %) as a clear oil.

1H NMR (CDCl3) δppm: 1.49(9H, s), 4.56(2H, s), 7.18-7.24(2H, m), 8.26(1H, dd, J=1.5, 3.6 Hz), 8.32(1H, d, J=2.9)

[0101]

(31-2) To a solution of 0.14 g of the compound from the process (31-1) (0.67 mmol) in dichloromethane (2 ml) was added 2 ml of trifluoroacetic acid, and the solution was stirred at room temperature for 3 hours. After evaporation, diisopropyl ether was added, and the precipitated solid was collected by filtration and dried to give 0.15 g of 3-pyridyloxyacetic acid trifluoroacetate (Yield: 83.8 %) as a light yellow solid.

1H NMR(DMSO-d6) δppm: 4.86(2H, s), 7.57(1H, dd, J=4.4, 8.1 Hz), 7.67(1H, ddd, J=1.5, 1.5, 8.8 Hz), 8.31(1H, d, J=5.1 Hz), 8.46(1H, d, J=2.1 Hz), 13(1H, br.s)

[0102]

(31-3) To a suspension of 100 mg of the compound from the process (31-2) (0.37 mmol) and 255 mg of the compound from Example 1, the process (1-4) (0.75 mmol) in dichloromethane (5 ml) was added 0.14 ml of triethylamine (1.0 mmol), and the mixture was cooled with ice. Under ice-cooling, to the mixture was added a solution of 140 mg of 2-chloro-N,N'-dimethylimidazolinium chloride (0.83 mmol) in dichloromethane (6 ml), and the mixture was warmed to room temperature with stirring for 7 hours, and left at room temperature overnight. After adding water and saturated brine, the mixture was extracted with chloroform.

[0103]

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel

(eluent: ethyl acetate:methanol = 10:1) to give 0.37 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)oxyacetylamino methyl]benzamide (Yield: quantitative) as a clear oil.

1H NMR(CDCl3) δ ppm: 1.52(9H, 5), 4.62(2H, s), 4.63(2H, d, J=7.3 Hz), 6.76(1H, br.s), 6.9-7.0(1H, br.s), 7.15-7.35(5H, m), 7.40(2H, d, J=8.1 Hz), 7.82(1H, d, J=8.1 Hz), 7.95(2H, d, J=8.1 Hz), 8.32(1H, dd, J=2.1, 4.4 Hz), 8.37(1H, d, J=2.8 Hz), 9.20(1H, br.s)

[0104]

(31-4) To a solution of 175 mg of the compound from the process (31-3) (0.37 mmol) in dioxane (2 ml) and methanol (2 ml) was added 4N hydrochloric acid-dioxane (2 ml), and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol and diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 90 mg of N-(2-aminophenyl)-4-[N-(pyridyl-3-yl) oxyacetylaminomethyl]benzamide (Yield: 64.6 %) as an opalescent solid.

1H NMR(DMSO-d6) δ ppm: 4.42(2H, d, J=5.9 Hz), 4.69(2H, s), 4.89(2H, br.s), 6.59(1H, dd, J=7.3, 8.1 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=7.3 Hz), 7.33-7.39(4H, m), 7.92(2H, d, J=8.1 Hz), 8.21(1H, dd, J=1.5, 4.4 Hz), 8.35(1H, d, J=2.9 Hz), 8.80(1H, br.t, J=5.9 Hz), 9.63(1H, br.s)

IR(KBr)cm: 3307, 1672, 1631, 1523, 1456, 1429, 1269, 1231, 803, 1756

[0105]

Example 32

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxycarbonyl] aminomethylbenzamide (Table 1: Compound 82)

(32-1) To a solution of 384 mg of 3-pyridylmethanol (3.52 mmol) in 5 ml of dry THF were added 523 mg of N,N'-carbonyldiimidazole (3.22 mmol) at room temperature. After stirring for an hour, to the mixture was added 1.0 g of the compound from Example 1, the process (1-4) (2.93 mmol) in 6 ml of dry THF.

[0106]

After being left at room temperature overnight, to the mixture was added 100 ml of chloroform, and the mixture was washed with water (3 x 20

ml) and saturated brine, and dried out with anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent:chloroform:methanol = 30:1) to give 1.27 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methoxycarbonyl]aminomethylbenzamide (Yield: quantitative) as an amorphous solid.

1H NMR (270 MHz, CDCl3) δ ppm:1.51(9H,s), 4.45(2H, d, J=5.9 Hz), 5.16(1H, s), 7.1-7.5(7H, m), 7.70(1H, d, J=8.1 Hz), 7.80(1H, d, J=7.3 Hz), 7.93(1H, d, J=8.1 Hz), 8.57(1H, d, J=4.4 Hz), 8.63(1H, s), 9.17(1H, s).

[0107]

(32-2) The compound from the process (32-1)(1.2 g, 2.8 mmol) was dissolved in 10 ml of methanol. To the solution was added 20 ml of 4N-hydrochloric acid-dioxane. The mixture was stirred at room temperature for 1.5 hours, and then poured into diluted sodium hydroxide aq. and extracted with chloroform (3 x 60 ml). The combined organic layer was washed twice with saturated brine, dried out with anhydrous magnesium sulfate and concentrated to give 0.88 g of crystals, which were then recrystallized from 16 ml of ethanol, to give 668 mg of N-(2-aminophenyl)-4-[(pyridin-3-yl) methoxycarbonyl]aminomethylbenzamide (Yield: 73 %).

[0108]

mp: 159-160 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.28(2H, d, J=5.9 Hz), 4.86(2H, s), 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=7 Hz), 6.97(1H, t, J=7 Hz), 7.17(1H, d, J=8 Hz), 7.3-7.5(3H, m), 7.78(1H, d, J=8 Hz), 7.93(2H, d, J=8 Hz), 8.53(1H, d, J=3.7 Hz), 8.59(1H, s), 9.61(1H, s).

IR(KBr)cm-1: 3295, 1648, 1541, 1508, 1457, 1309, 1183, 742

As described in Example 32, the compounds of Examples 33 to 53 were prepared, each of whose melting point (mp), 1H NMR data, IR data are shown below.

[0109]

Example 33

N-(2-aminophenyl)-4-(benzyloxycarbonyl)aminomethylbenzamide (Table 1: Compound 11)

mp: 174-178 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.28(2H, d, 5.9), 4.89(2H, br.s), 5.06(2H, s), 6.59(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.3-7.4(6H, m), 7.93(3H, m), 9.63(1H, s).

IR(KBr)cm-1: 3332, 1687, 1652, 1536, 1456, 1279, 747

[0110]

Example 34

N-(2-aminophenyl)-4-[(4-(imidazol-1-yl)benzyl)oxycarbonyl]aminomethylbenzamide (Table 1: Compound 47)

mp: 195-198 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.29(2H, d, J=6.6 Hz), 4.88(2H, s), 5.10(2H, s), 6.60-6.63(1H, m), 6.78(1H, d, J=8.1 Hz), 6.97(1H, t, J=7.3 Hz), 7.11(1H, s), 7.16(1H, d, J=7.3 Hz), 7.37(2H, d, J=8.1 Hz), 7.49(2H, d, J=8.8 Hz), 7.66(2H, d, J=8.1 Hz), 7.74(1H, s), 7.92-7.96(3H, m), 8.25(1H, s), 9.62(1H, s)

[0111]

Example 35

N-(2-aminophenyl)-4-[(pyridin-2-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 51)

mp: 166-167 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.30(2H, d, 5.9), 4.88(2H, br.s), 5.12(2H, s), 6.60(1H, dd, 7.3, 8.1) , 6.78(1H, d, 8.1), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 7.3), 7.33(1H, dd, 3.7, 7.3), 7.40(3H, d, 8.1), 7.83(1H, ddd, 1.5, 7.3, 8.1), 7.94(2H, d, 8.1), 8.03(1H, t, 5.9), 8.55(1H, d, 5.1), 9.62(1H, br.s)

IR(KBr)cm-1: 3334, 1694, 1632, 158, 1276, 755

[0112]

Example 36

N-(2-aminophenyl)-4-[2-(pyridin-2-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 52)

mp: 146-148 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.04(2H, t, 6.6), 4.23(2H, d, 5.9), 4.36(2H, t, 6.6), 4.88(2H, br.s), 6.60(1H, dd, 7.3, 8.1), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.15-7.30(3H, m), 7.34(2H, d, 8.1), 7.69 -7.77(2H, m), 7.92(2H, d, 7.3), 8.50(1H, d, 4.4), 9.62(1H, br.s)

IR(KBr)cm-1: 3330, 1690, 1633, 1594, 1524, 1277, 760

[0113]

Example 37

N-(2-aminophenyl)-4-[(6-methylpyridin-2-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 59)

mp: 138 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.47(3H, s), 4.30(2H, d, J=5.9), 5.07(4H, s), 6.63(1H, t, J=8.1), 6.80 (1H, d, J= 7.34), 6.98(1H, t, J=8.1), 7.18(3H, d, J=7.3), 7.40(2H, d, J=8.1), 7.71(1H, t, J=8.1), 7.94(2H, d, J=8.1), 8.03(1H, t, J=5.9), 9.66(1H, s)

IR(KBr)cm-1: 1259, 1634, 1693, 3335.

[0114]

Example 38

N-(2-aminophenyl)-4-[(2-(pyridin-3-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 83)

mp: 120-125 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.91(2H, t, J=6.60), 4.22(4H, t, J=6.6), 4.89(2H, s), 6.55-6.63(1H, m), 6.78(1H, dd, J=8.1, 1.5), 6.97(1H, t, J=6.6), 7.17(1H, d, J=6.6), 7.33(3H, d, J=8.1), 7.69(1H, d, J=8.1), 7.79(1H, t, J=6.6), 7.93(2H, d, J=8.0), 8.43-8.49(2H, m), 9.62(1H, s)

IR(KBr)cm-1: 1260, 1655, 1705, 3234

[0115]

Example 39

N-(2-aminophenyl)-4-[3-(pyridin-3-yl)propyloxycarbonyl]aminomethyl benzamide (Table 1: Compound 84)

mp: 121-124 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.83-1.94(2H, m), 2.67(2H, t, 7.3), 3.98(2H, t, 6.6), 4.26(2H, d, 5.9), 4.89(2H, br.s), 6.60(1H, dd, 8.1, 8.1), 6.78(1H, d, 7.3), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 8.1), 7.29-7.33(1H,m), 7.37(1H, d, 8.1), 7.64(1H, d, 8.1), 7.81(1H, dd, 5.9, 6.6), 7.94(2H,d, 8.1), 8.40-8.44(2H,m), 9.63(1H, br.s)

IR(KBr)cm-1: 3348, 1696, 1635, 1523, 1458, 1302, 1272, 1141, 1019, 754, 713

[0116]

Example 40

N-(2-aminophenyl)-4-[(2-methylpyridin-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 92)

mp: 164-165 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.49(3H, s), 4.28(2H,d, J=6.6), 4.89(2H, s), 5.10(2H, s), 6.60(1H, t, J=6.6), 6.78(1H, d, J=8.1), 6.9(1H, t, J=7.3), 7.17(1H, d, J=7.3), 7.21-7.26(1H, m), 7.37(2H, d, J=8.1), 7.68(1H, d, J=6.6), 7.92-8.00(3H, m), 8.39(1H, d, J=4.4), 9.62(1H, s)

IR(KBr)cm-1: 1260, 1630, 1719, 3332

[0117]

Example 41

N-(2-aminophenyl)-4-[(6-methylpyridin-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 94)

mp: 164-165 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.46(3H, s), 4.27(2H, d, J=6.6), 4.88(2H, s), 5.05(2H, s), 6.59(1H, dt, J=8.1, 1.5), 6.78(1H, dd, J=8.1, 1.5), 6.97(1H, dt, J=7.3, 1.5), 7.17(1H, d, J=7.3), 7.26(1H, d, J=8.1), 7.36(2H, d, J=8.1), 7.67(1H, dd, J=8.1, 2.2), 7.93(3H, d, J=8.1), 8.45(1H, d, J=1.5), 9.62(1H, s)

IR(KBr)cm-1: 1260, 1632, 1701, 3293

[0118]

Example 42

N-(2-aminophenyl)-4-[(2-chloropyridin-3-yl)methoxycarbonyl]aminom ethylbenzamide (Table 1: Compound 106)

mp: 159-169 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.30(2H, d, J=5.9), 5.00(2H, s), 5.13(2H, s), 6.61(1H, t, J=7.34), 6.79(1H, dd, J=8.1, 1.5), 6.98(1H, dt, J=7.3, 1.5), 7.17(1H, d, J=6.6), 7.39(2H, d, J=8.8), 7.47-7.52(1H, m), 7.91-7.96(3H, m), 8.08(1H, t, J=5.9), 8.40(1H, dd, J=4.4, 1.5), 9.64(1H, s)

IR(KBr)cm-1: 1273, 1632, 1702, 3340

[0119]

Example 43

N-(2-aminophenyl)-4-[(6-chloropyridin-3-yl)methoxycarbonyl]aminom ethylbenzamide (Table 1: Compound 108)

mp: 180-185 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.24(2H, d, J=5.9), 4.89(2H, br.s) , 5.10(2H, s), 6.60(1H, t, J=7.3), 6.78(1H, d, J=8.1), 6.97(1H, dt, J=8.1, 1.5), 7.16(1H, d, J=6.6), 7.37(2H, d, J=8.1), 7.56(1H, d, J=8.1), 7.85-8.02(4H, m),

8.44(1H, d, J=2.2), 9.62(1H, s)

IR(KBr)cm-1: 1271, 1533, 1696, 3282, 3346

[0120]

Example 44

N-(2-aminophenyl)-4-[(pyridin-4-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 121)

mp: 180-183 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.30(2H, d, 6.6), 4.89(2H, s), 5.12(2H, s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, dd, 1.5, 7.3), 6.97(1H, ddd, 1.5, 7.3, 8.1), 7.16(1H, d, 7.3), 7.34(2H, d, 5.9), 7.39(2H, d, 8.1), 7.94(2H, d, 8.1), 8.09(1H, t, 5.9), 8.57(1H, d), 9.64(1H, br.s)

IR(KBr)cm-1: 3394, 3290, 1711, 1645, 1624, 1535, 1504, 1321, 1251, 1138, 1049, 763

[0121]

Example 45

N-(2-aminophenyl)-4-[2-(thiophen-3-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 136)

mp: 128-138 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 2.90(2H, t, J=7.3), 4.17-4.26(4H, m), 4.89(2H, s), 6.60(1H, t, J=8.1), 6.78(1H, d, J=6.6), 6.97(1H, t, J=7.3), 7.06(1H, d, J=5.1), 7.17(1H, d, J=7.3), 7.26(1H, s), 7.36(2H, d, J=8.1), 7.47(1H, t, J=2.2), 7.81(1H, t, J=5.9), 7.93(2H, d, J=8.1), 9.63(1H, s).

IR(KBr)cm-1: 1252, 1638, 1716, 3314

[0122]

Example 46

N-(2-aminophenyl)-4-[(3-phenyloxazol-5-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 141)

mp: 192-195 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.30(2H, d, J=5.9), 4.89(2H, s), 5.25(2H, s), 6.60(1H, t, J=6.6), 6.68(1H, d, J=8.1), 6.94(1H, t, J=7.3), 7.09(1H, s), 7.16(1H, d, J=7.3), 7.39(2H, d, J=8.1), 7.51(4H, d, J=2.2), 7.87-7.96(5H, m), 8.12(1H, t, J=5.9), 9.63(1H, s)

IR(KBr)cm-1: 1262, 1630, 1718, 3292

[0123]

Example 47

N-(2-aminophenyl)-4-[(thiazol-5-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 147)

mp: 168-175 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.28(2H, d, 5.9), 4.91(2H, br.s), 5.30(2H, s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1), 7.16(1H, d, 7.3), 7.36(2H, d, 8.1), 7.91-8.00(4H, m), 9.09(1H, s), 9.63(1H, s)

IR(KBr)cm-1: 3346(br.), 1697, 1636, 1525, 1456, 1271, 873, 753

[0124]

Example 48

N-(2-aminophenyl)-4-[2-(4-methylthiazol-5-yl)ethoxycarbonyl]aminomethylbenzamide (Table 1: Compound 148)

mp: 130-133 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 2.32(3H, s), 3.07(2H, t, J=5.9), 4.15(2H, t, J=5.9), 4.25(2H, d, J=6.6), 4.89(2H, s), 6.60(1H, t, J=5.9), 6.78(1H, dd, J=7.3, 1.5), 6.97(1H, dt, J=7.3, 1.5), 7.16(1H, d, J=8.1), 7.35(2H, d, J=8.1), 7.83(1H, t, J=5.9), 7.94(2H, d, J=8.1), 8.85(1H, s), 9.62(1H, s)

IR(KBr)cm-1: 1270, 1635, 1691, 3350

[0125]

Example 49

N-(2-aminophenyl)-4-[(1-methylpiperidin-3-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 152)

mp: 130-135 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 1.49-1.78(3H, m), 1.83-2.01(3H, m), 2.30(3H, s), 2.85(2H, t), 3.74-3.94(2H, m), 4.25(2H, d, J=5.8), 6.55-6.62(3H, m), 6.78(1H, d, J=8.1), 6.97(1H, t, J=7.3), 7.16(1H, d, J=8.1), 7.37(2H, d, J=8.1), 7.79(1H, t, J=6.6), 7.93(2H, d, J=8.0), 9.66(1H, s)

IR(KBr)cm-1: 1263, 1648, 1702, 2722, 3323

[0126]

Example 50

N-(2-aminophenyl)-4-[(4-methylpiperazin-1-yl)methoxycarbonyl]aminomethylbenzamide (Table 1: Compound 153)

mp: 145-155 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 1.73(2H, t, J=6.6), 2.36-2.63(13H, m),

4.00(2H, t, J=6.6), 4.30(2H, d, J=5.8), 6.55-6.63(4H, m), 6.78(1H, d, J=6.6), 6.97(1H, t, J=7.3), 7.16(1H, d, J=7.3), 7.37(2H, d, J=8.7), 7.73(1H, t, J=5.9), 7.94(2H, d, J=8.0), 9.66(1H, s)

IR(KBr)cm-1: 1262, 1701, 2706, 3341

[0127]

Example 51

N-(2-aminophenyl)-4-[(tetrahydrofuran-3-yl)methoxycarbonyl]amino methylbenzamide (Table 1: Compound 155)

1H NMR(DMSO-d6) δ ppm: 1.50-1.60(1H, m), 1.88-2.00(1H, m), 2.44-2.54(1H, m), 3.41-3.47(1H, m), 3.56-3.77(3H, m), 3.85-4.04(2H, m), 4.25(2H, d, J=5.9 Hz), 4.89(2H, s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1), 6.97(1H, dd, J=7.3, 8.1 Hz), 7.17(1H, d, J=8.1), 7.37(2H, d, J=8.1 Hz), 7.81(1H, t, J=5.9 Hz), 7.94(2H, d, J=8.1), 9.62(1H, br.s)

IR(KBr)cm-1: 3349, 1695, 1635, 1523, 1457, 1259, 754

[0128]

Example 52

N-(2-aminophenyl)-4-(phenoxycarbonyl)aminomethylbenzamide (Table 1: Compound 12)

mp: 174-175 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.36(2H, d, 5.9), 4.90(2H,br.s), 6.60(1H,dd, 7.3, 7.3), 6.77(1H, dd, 7.3, 7.3), 6.98(1H, ddd, 1.5, 7.3, 7.3), 7.05-7.24(4H, m), 7.39-7.46(4H, m), 7.97(2H, d, 8.1), 8.41(1H, t, 5.9), 9.65(1H, br.s)

IR(KBr)cm-1: 3443, 3362, 3313, 1732, 1706, 1636, 1527, 1493, 1458, 1305, 1217, 748

[0129]

Example 53

N-(2-aminophenyl)-4-[(pyridin-3-yl)oxycarbonyl]aminomethylbenzamide (Table 1: Compound 81)

mp: 209 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.38(2H, d, 6.6), 4.90(2H, br.s) , 6.55-6.63(1H, m), 6.78(1H, d, 8.1), 7.00(1H, dd, 7.3, 7.3), 7.17(1H, d, 8.8), 7.37-7.47(3H, m), 7.64(1H, d, 8.8), 7.97(2H, d, 8.1), 8.43(2H, d, 3.1), 8.59(1H, t, 5.9), 9.66(1H, br.s)

[0130]

Example 54

N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxythiocarbonyl]aminomethylbenzamide (Table 1: Compound 86)

(54-1) To a solution of 20 mg of 3-pyridylmethanol (0.18 mmol) in 5 ml of dry THF were added 30 mg of N,N'-thiocarbonyldiimidazole (0.16 mmol) at room temperature. After stirring overnight, to the mixture were added 50 mg of the compound from Example 1, the process (1-4) (0.14 mmol).

[0131]

After leaving at room temperature overnight, to the solution was added 100 ml of chloroform, and the solution was washed with water (3 x 20 ml) and then saturated brine, and dried out with anhydrous magnesium sulfate. After evaporation, the residue was purified by column chromatography on silica gel (eluent: chloroform:methanol = 30:1) to give 70 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methoxythiocarbonyl]aminomethylbenzamide (Yield: 88 %) as amorphous.

1H NMR(270 MHz, DMSO-d6) δppm: 1.45(9H, s), 4.73(2H, d, J=5.9 Hz), 5.52(2H, s), 6.73-7.33(3H, m), 7.35-7.43(2H, m), 7.58-7.95(5H, m), 8.14-8.65 (3H, m), 9.80(1H, s), 9.91(1H, t)

[0132]

(54-2) 50 mg of the compound from the process (54-1) (0.10 mmol) was dissolved in 3 ml of methanol. To the solution was added 3 ml of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 1.5 hours. The mixture was poured into diluted sodium hydroxide aq. to neutralize the residual hydrochloric acid, and then was extracted with chloroform (3 x 10 ml). The organic layer was washed twice with saturated brine, dried out with anhydrous magnesium sulfate and concentrated to give 34 mg of N-(2-aminophenyl)-4-[(pyridin-3-yl)methoxythiocarbonyl] aminomethylbenzamide (Yield: 87 %).

mp: 154-156 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 4.73(2H, d, J=5.9 Hz), 4.88(2H, s), 5.52(2H, s), 6.60(1H, t, J=7.3 Hz), 6.77(1H, d, J=8.1 Hz), 6.96(1H, t, J=8.1 Hz), 7.16(1H, d, J=7.3 Hz), 7.29-7.41(3H, m), 7.83-7.95(3H, m), 8.50-8.56(1H, m),

8.65(1H, s), 9.62(1H, s), 9.93(1H, t)

[0133]

Example 55

Preparation of N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl) ureidomethyl]benzamide (Table 1: Compound 88)

(55-1) To a solution of 3-picolylamine (0.28g, 2.6 mmol) in THF (10 ml) was added N,N'-carbonyldiimidazole (0.42 g, 2.4 mmol) at room temperature, and the mixture was stirred for an hour. To the solution was added the compound from Example 1, the process (1-4) (0.58 g, 1.8 mmol) at room temperature, and the solution was stirred for 3 hours and then left overnight.

[0134]

After diluting with water, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:methanol = 10:1) to give N-[2-(N-tert-butoxycarbonyl) amino]phenyl-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (0.77 g, Yield: 90 %) as a white amorphous solid.

1H NMR(270MHz, CDCl3) δ ppm: 1.46(9H, s), 4.20(2H, d, 5.1), 4.28(2H, d, 4.3),6.1-6.3(2H, m), 7.0-7.25(4H, m), 7.33(1H, d, 7.3), 7.49-7.54(2H, m), 7.58-7.64(3H, m), 7.75(1H, s), 8.28(1H, br.s), 8.39(1H, d, 5.1), 9.65 (1H, br.s)

[0135]

(55-2) To a solution of the compound from the process (55-1)(0.63 g, 1.32 mmol) in dioxane (4 ml) and methanol (2 ml) was added 4N hydrochloride-dioxane (4 ml), and the mixture was stirred at room temperature for 2 hours. After adding saturated sodium bicarbonate aq., the mixture was extracted with ethyl acetate-methyl ethyl ketone. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether to give N-(2-aminophenyl)-4-[N'-(pyridin-3-ylmethyl)ureidomethyl]benzamide (0.37 g, Yield: 74.7 %) as a brown solid.

[0136]

mp: 167-175 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.27(2H, d, 5.9), 4.31(2H, d, 5.9), 4.89(2H, br.s), 6.57-6.63(3H, m), 6.78(1H, d, 8.1), 6.97(1H, dd, 7.3, 8.1),

7.17(1H, d, 7.3), 7.32-7.38(3H, m), 7.66(1H, d, 8.1), 7.93(2H, d, 8.1), 8.44(1H, d, 5.1), 8.49(1H, d, 2.1), 9.63(1H, br.s)

IR(KBr)cm-1: 3344, 3241, 1645, 1560, 1527, 1505, 1283, 751, 708

[0137]

As described in Example 55, the compounds of Examples 56 to 59 were prepared, each of whose melting point (mp), 1H NMR data, IR data are shown below.

Example 56

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)ureidomethyl]benzamide (Table 1: Compound 24)

mp: 206-208 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 4.35(2H, d,J=5.9 Hz), 4.93(4H, br.s), 6.13(1H, d, J=7.3 Hz), 6.51-6.62(3H, m), 6.74-6.98(3H, m), 7.12-7.18(1H, m), 7.41(2H,d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 8.28(1H, s), 9.61(1H, s)

[0138]

Example 57

N-(2-aminophenyl)-4-[N'-(pyridin-3-yl)ureidomethyl]benzamide (Table 1: Compound 87)

mp: 187-190 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 4.39(2H, d, 5.9), 4.89(2H,br.s), 6.59(1H, d, 7.3, 7.3), 6.77(1H, d, 6.6), 6.88(1H, t, 5.9), 6.97(1H, ddd, 1.5, 6.6, 7.3 Hz), 7.16(1H, d, 8.1), 7.26(1H, dd, 4.4, 8.1), 7.42(2H, d, 8.8), 7.95(2H, d, 8.1), 7.89-7.96(1H, m), 8.12(1H, dd, 1.5, 4.4), 8.56(1H, d, 3.0), 8.85(1H, s), 9.62(1H, s)

IR(KBr)cm-1: 3248, 1663, 1541, 1423, 1280, 1054

[0139]

Example 58

N-(2-aminophenyl)-4-[N'-(3-aminophenyl)thioureidomethyl]benzamide (Table 1: Compound 25)

mp: 123 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 4.80(2H, d, J=5.1 Hz), 4.87(2H, s), 5.12(2H, s), 6.36(1H, dd, J=1.5, 8.1 Hz). 6.48-6.63(3H, m), 6.78(1H, d, J=6.6 Hz), 6.94-7.00(2H, m), 7.17(1H, d, J=8.1 Hz), 7.42(2H, d, J=8.1 Hz), 7.92-8.01(3H, m), 9.46(1H, s), 9.61(1H, s)

[0140]

Example 59

N-(2-aminophenyl)-4-[N'-(3-nitrophenyl)thioureidomethyl]benzamide (Table 1: Compound 20)

mp: 160 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.87(2H, d, J=5.1 Hz), 7.27-7.33(3H, m), 7.46-7.63(5H, m), 7.89-7.95(2H, m), 8.05(2H, d, J=8.1 Hz), 8.70(1H,s), 8.84(1H, t, J=8.9 Hz), 10.37 (1H, s)

[0141]

Example 60

Preparation of N-(2-aminophenyl)-4-[2-(N-(pyridin-3-ylacetyl)amino) ethyl]benzamide (Table 1: Compound 77)

(60-1) To a suspension of 3.40 g of terephthalaldehydic acid (22.6 mmol) in toluene (25 ml) was added thionyl chloride (4 ml), and the mixture was heated with stirring at for 2 hours. After cooling and evaporation, the residue was dissolved in THF (50 ml) to give a solution of the acid chloride. To a solution of 4.16 g of the compound from Example 1, the process (1-2) (20.0 mmol) in THF (10 ml) was added triethylamine (6 ml, 42.8 mmol) and then the above solution of the acid chloride was added dropwise under ice-cooling for 30 min.

[0142]

After stirring for 5 hours, to the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (gradient elution with chloroform to chloroform:ethyl acetate = 10:1) to give 3.42 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-formylbenzamide (Yield: 50.2 %) as a light brown solid.

1H NMR(CDCl3) δ ppm: 1.52(9H, s), 6.77(1H, br.s), 7.16-7.18(2H, m), 7.23-7.26(1H, m), 7.88(1H, d, J=8.8 Hz), 7.98(2H, d, J=8.8 Hz), 8.13(2H, d, J=8.8 Hz), 9.57(1H, br.s), 10.11(1H, br.s)

IR(KBr)cm-1: 3326, 3251, 1707, 1696, 1659, 1603, 1165

[0143]

(60-2) A suspension of 3.0 g of the compound from the process (60-1)

(8.82 mmol) and 4.5 g of ethoxycarbonylmethyl triphenylphosphine (12.9 mmol) in toluene (10 ml) was stirred in a stream of nitrogen at 80 ℃ for 5.5 hours. After cooling, the mixture was diluted with ethyl acetate; washed with saturated sodium bicarbonate aq., water and saturated brine, and dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate = 20:1) to give 3.3 g of ethyl 4-(N-2-(N-tert-butoxycarbonyl)aminophenyl)aminocarbonylcinnamate (Yield: 91.1 %) as a yellow amorphous solid.

1H NMR(CDCl3) δ ppm: 1.35(3H, t, J=7.3 Hz), 1.52(9H, s), 4.28(2H, q, J=7.3 Hz), 6.52(1H, d, J=15.1 Hz), 6.80(1H, br.s), 7.16-7.25(3H, m), 7.61(2H, d, J=8.1 Hz), 7.71(1H, d, J=15.1 Hz), 7.82(1H, d, 7.3), 7.98(2H, d, J=8.1 Hz), 9.34 (1H, br.s)

[0144]

(60-3) To a solution of 2.50 g of the compound from the process (60-2) (6.09 mmol) in THF (30 ml) and methanol (40 ml) was added 10 % Pd/C (wet, 0.5 g) in a stream of nitrogen, and then stirred in a stream of hydrogen for 30 min. After filling with nitrogen, the mixture was filtered to remove the catalyst, and the filtrate was evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 2.23 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(2-ethoxycarbonyl)ethylbenzamide (Yield: 88.8 %) as a white solid.

1H NMR(CDCl3) δ ppm: 1.25(3H, t, J=7.3 Hz), 1.52(9H, s), 2.65(2H, t, J=7.3 Hz), 3.02(2H, t, J=7.3 Hz), 4.13(2H, q, J=7.3 Hz), 6.77(1H, br.s), 7.16-7.33(5H, m), 7.78(1H, d, J=8.1 Hz), 7.89(2H, d, J=8.8 Hz), 9.06(1H, br.s)

[0145]

(60-4) To a suspension of 2.21 g of the compound from the process (60-3) (5.36 mmol) in methanol (10 ml) and water (15 ml) was added 0.37 g of lithium hydroxide monohydrate (8.82 mmol), and the mixture was stirred at 40 ℃ for 3 hours. After cooling, to the mixture was added 10 % hydrochloric acid and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diisopropyl ether, and the precipitated solid was filtered and dried to give 1.87 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(2-carboxyethyl)benzamide (Yield: 90.8 %) as a white solid.

1H NMR(DMSO-d6) δppm: 1.45(9H, s), 2.59(2H, t, J=7.3 Hz), 2.91(2H, t, J=7.3 Hz), 7.13-7.20(2H, m), 7.40(2H, d, J=8.1 Hz), 7.54(2H, dd, J=7.3, 2.1), 7.88(2H, d, J=8.1 Hz), 8.66(1H, br.s), 8.66(1H, br.s), 9.79(1H, br.s)

[0146]

(60-5) To a suspension of 0.12 g of the compound from the process (60-4) (0.3 mmol) in benzene (5 ml) were added 0.1 ml of triethylamine (0.7 mmol) and 0.3 g of molecular sieves 4A, and the mixture was stirred in a stream of nitrogen for 0.5 hours. To the mixture was added 0.15 ml of diphenylphosphoryl azide (0.7 mmol), and the mixture was refluxed with heating for 2 hours. After cooling, to the mixture was added 0.4 ml of benzyl alcohol (3.8 mmol), and the mixture was refluxed with heating for additional 2.5 hours. After diluting with ethyl acetate, the reaction mixture was washed with water and saturated brine.

[0147]

The organic layer was dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:ethyl acetate = 4:1) to give 129 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl] -4-(N-benzyloxycarbonyl)aminoethylbenzamide (Yield: 88 %) as a clear oil.

1H NMR(CDCl3) δppm: 1.51(9H, s), 2.89(2H, t, J=7.3 Hz), 3.45-3.54(2H, m), 4.8(1H, m), 5.10(2H, s),6.76(1H, br.s), 7.20-7.38(10H, m), 7.79(1H, d, J=8.8 Hz), 7.89(2H, d, J=8.1 Hz), 9.10(1H, br.s)

[0148]

(60-6) To a solution of 129 mg of the compound from the process (60-5) (0.26 mmol) in methanol (10 ml) was added 10 % Pd/C (wet, 0.05 g) in a stream of nitrogen, and then stirred in a hydrogen stream for 2 hours. After removing the catalyst, the filtrate was evaporated and dried. The residue was dissolved in dichloromethane (5ml). To the solution were added 0.18 g of 3-pyridineacetic acid hydrochloride (1.04 mmol) and then 0.28 g of triethylamine (2.0 mmol), and the mixture was ice-cooled. Under ice-cooling, to the mixture was added 0.17 g of 2-chloro-N,N'-dimethylimidazolinium chloride (1.0 mmol), and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated.The residue was purified by column chromatography on silica

gel (eluent: ethyl acetate:methanol = 10:1) to give 50 mg of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-(N-(pyridin-3-ylacetyl)amino) ethyl]benzamide (Yield: 40 %) as a colorless oil.

[0149]

1H NMR (CDCl3) δ ppm: 1.48(9H, s), 2.80(2H, t, J=6.6 Hz), 3.42(2H, m), 3.52(2H, s), 6.33(1H, t-like, J=5.9 Hz), 7.09(2H, d, J=8.1 Hz), 7.14-7.20(2H, m), 7.24(1H, dd, J=4.4, 7.3Hz), 7.41(1H, dd, J=3.7, 5.9 Hz), 7.50(1H, s), 7.58(1H, dd, J=1.5, 5.9 Hz), 7.69(1H, dd, J=3.7, 5.9Hz), 7.75(2H, d, J=8.1 Hz), 8.22(1H, d, J=2.1 Hz), 8.44(1H, dd, J=1.5, 4.4 Hz), 9.49(1H, br.s)

[0150]

(60-7) To a solution of 50 mg of the compound from the process (60-6) (0.10 mmol) in dioxane (2 ml) and methanol (1 ml) was added 4N hydrochloric acid-dioxane (2 ml), and the mixture was stirred at room temperature for 2.5 hours. To the mixture was added saturated sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was dried to give 22 mg of N-(2-aminophenyl)-4-[2-(N-(pyridin-3-ylacetyl)amino)ethyl]benzamide (Yield: 59 %) as an amorphous solid.

[0151]

1H NMR(DMSO-d6) δ ppm: 2.7-2.9(4H, m), 3.42(2H, s), 4.89(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=7.3, 7.3 Hz), 7. 16(1H, d, J=7.3 Hz), 7.29-7.32(3H, m), 7.59(1H, d, J=8.1 Hz), 7.89(1H, d, J=8.1 Hz), 8.22(1H, t-like), 8.41-8.43(2H, m), 9.62(1H, br.s)

[0152]

Example 61

Preparation of N-(2-aminophenyl)-4-[2-(N-(3-picolyl)aminocarbonyl) ethyl]benzamide (Table 1: Compound 80)

(61-1) To a suspension of 0.58 g of the compound from Example 60, the process (60-4) (1.5 mmol) in dichloromethane (5 ml) were added 0.22 g of 3-picolylamine (2.0 mmol) and 0.56 ml of triethylamine (4.0 mmol). Under ice-cooling, to the mixture was added 0.39 g of 2-chloro-N,N'-dimethylimidazolinium chloride (2.0 mmol) in dichloromethane (5 ml), and the mixture was stirred for 1.5 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

[0153]

The organic layer was washed with water and saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:methanol:NH_3 aq. = 100:10:1) to give 0.71 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[2-(N-(3-picolyl)aminocarbonyl)ethyl]benzamide (Yield: 94 %) as a light brown oil.

1H NMR(CDCl3) δ ppm: 1.45(9H, s), 2.42(2H, t, J=7.3 Hz), 2.98(2H, t, J=7.3 Hz), 4.32(2H, d, J=6.6 Hz), 6.44(1H, t, J=6.6 Hz), 7.14-7.27(5H, m), 7.48-7.57(3H, m), 7.63-7.68(3H, m), 7.90(1H, d, J=2.1 Hz), 8.43(1H, dd, J=1.4, 4.4 Hz), 9.86(1H, br.s)

[0154]

(61-2) To a solution of 0.70 g of the compound from the process (61-1) (1.47 mmol) in dioxane (5 ml) was added 4N hydrochloride-dioxane (5 ml) and then methanol (2 ml), and the mixture was stirred at room temperature for 2 hours. To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.42 g of N-(2-aminophenyl)-4-[2-(N-(3-picolyl)aminocarbonyl) ethyl]benzamide (Yield: 76.3 %) as an opalescent solid.

[0155]

mp: 168-170 ℃

1H NMR(DMSO-d6) δ ppm: 2.47-2.53(2H, m), 2.93(2H, t, J=7.3 Hz), 4.27(2H, d, J=5.9 Hz), 4.90(2H, br.s), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.16(1H, d, J=6.6 Hz), 7.28-7.35(1H, m), 7.33(2H, d, J=8.1 Hz), 7.49(1H, dd, J=2.1, 5.9 Hz), 7.89(2H, d, J=8.1 Hz), 8.39-8.44(3H, m), 9.62(1H, br.s)

IR(KBr)cm-1: 3313, 1641, 1523, 1457, 1300, 748, 713

[0156]

Example 62

Preparation of N-(2-aminophenyl)-4-[(pyridin-3-yl) methylaminocarbonyloxy]methylbenzamide (Table 1: Compound 85)

(62-1) To a solution of methyl 4-hydroxymethylbenzoate (1.99 g, 12.0

mmol) in THF (20 ml) were added 1.78 g of N,N'-carbonyldiimidazole (11.0 mmol) at room temperature, and the solution was stirred for an hour. To the solution were added 1.08 g of 3-picolylamine (10.0 mmol) at room temperature, and the mixture was stirred for 3.5 hours and left overnight. Water was added to the solution, and the mixture was extracted with ethyl acetate.

[0157]

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 2.76 g of N-(4-methoxycarbonyl) benzyloxycarbonyl-3-picolylamine (Yield: 91.9 %) as a white waxy solid.

1H NMR(CDCl3) δ ppm: 3.91(3H, s), 4.40(2H, d, J=5.9Hz), 5.18(2H, s), 5.5(1H, br.s), 7.24-7.28(1H, m), 7.40(2H, d, J=8.1 Hz), 7.65(1H, d, J=7.3 Hz), 8.02(2H, d, J=8.8 Hz), 8.50-8.53(2H, m)

[0158]

(62-2) To a suspension of 2.40 g of the compound from the process (62-1) (8.0 mmol) in methanol (10 ml) and water (20 ml) was added 0.42 g of lithium hydroxide monohydrate (10.0 mmol), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added 10 % hydrochloric acid to acidified to pH 2 to 4, and the precipitated solid was collected by filtration and dried to give 1.83 g of N-(4-carboxy) benzyloxycarbonyl-3-picolylamine (79.9 %) as a white solid.

1H NMR(DMSO-d6) δ ppm: 4.24(2H, d, J=5.9 Hz), 5.13(2H, s), 7.33-7.38 (1H, m), 7.46(2H, d, J=8.1 Hz), 7.94(2H, d, J=8.1 Hz), 7.95-8.01(1H, m), 8.46(1H, d, J=5.1 Hz), 8.49(1H, d, J=1.5 Hz), 13.0(1H, br.s)

[0159]

(62-3) To a suspension of 1.26 g of the compound from the process (62-2) (4.4 mmol) in dichloromethane (20 ml) were slowly added 1.0 ml of oxalyl chloride (11.4 mmol) and then several drops of DMF. The reaction mixture was stirred at room temperature for 10 min. and at 40 ℃ for additional 30 min. After cooling, the mixture was evaporated and the excess oxalyl chloride was removed by evaporation with toluene. To the residue was added dichloromethane (10 ml). Under ice-cooling, to the mixture was then added dropwise a solution of 0.83 g of the compound from Example 1, the process (1-2) (4.0 mmol) in dichloromethane (8 ml) and pyridine (8 ml), and

the solution was warmed to room temperature with stirring for 7 hours and left overnight.

[0160]

To the mixture was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform. The organic layer was washed with saturated brine, dried and evaporated. Toluene was added to the residue to azeotropically remove the excess pyridine. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to give 1.40 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[(pyridin-3-yl)methylaminocarbonyloxy]methylbenzamide (Yield: 73.4 %) as a light brown solid.

1H NMR (CDCl3) δ ppm: 1.51(9H, s), 4.40(2H, d, J=5.9 Hz), 5.19(2H, s), 5.56(1H, m), 7.07(1H, br.s), 7.14-7.31(4H, m), 7.43(2H, d, J=8.1 Hz), 7.65(1H, d, J=8.1 Hz), 7.76(1H, d, J=7.3 Hz), 7.95(2H, d, J=8.1 Hz), 8.52(2H, d, J=4.1 Hz), 9.32(1H,br.s)

[0161]

(62-4) To a solution of 1.00 g of the compound from the process (62-3) (2.10 mmol) in dioxane (10 ml) and methanol (2 ml) was added 4N hydrochloric acid-dioxane (9 ml) at room temperature, and the mixture was stirred for 2 hours. To the mixture was added saturated sodium bicarbonate aq. and the mixture was extracted with ethyl acetate-methyl ethyl ketone (1:1). The organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 0.79 g of N-(2-aminophenyl)
-4-[(pyridin-3-yl)methylaminocarbonyloxy]methylbenzamide (Yield: quantitative) as a white solid.

mp: 139-141 ℃

1H NMR(DMSO-d6) δ pm: 4.25(2H, d, J=5.9 Hz), 4.90(2H, s), 5.13(2H, s), 6.60(1H, dd, J=6.6, 7.3 Hz), 6.78(1H, d, J=7.3 Hz), 6.97(1H, dd, J=6.6, 7.3 Hz), 7.17(1H, d, J=7.3 Hz), 7.36(1H, dd, J=4.4, 8.1 Hz), 7.47(2H, d, J=8.1 Hz), 7.67(1H, d, J=8.1 Hz), 7.97(2H, d, J=7.3 Hz), 7.9-8.0(1H, m), 8.46(1H, dd, J=1.5, 5.1 Hz), 8.49(1H, d, J=2.1 Hz), 9.65(1H, br.s)

IR(KBr)cm-1: 3326(br.), 1694, 1637, 1526, 1458, 1147, 750, 712

[0162]

Example 63

Preparation of N-(2-aminophenyl)-4-[3-(imidazol-1-yl) propylaminocarbonyloxy]methylbenzamide (Table 1: Compound 146)

The titled compound was prepared as described in Example 62.

mp: (amorphous)

1H NMR(270 MHz, DMSO-d6) δppm: 1.80-1.89(2H, m), 2.94-3.02(2H, m), 3.98(2H, t, J=7.3 Hz), 4.88(2H, s), 5.11(2H, s), 6.55-6.63(1H, m), 6.76-6.97(3H, m), 7.10-7.18(2H, m), 7.43-7.48(3H, m), 7.61(1H, s), 7.98(2H, d, J=8.1 Hz), 9.66(1H, s)

[0163]

Example 64

N-(2-aminophenyl)-4-(phenylacetylamino)benzamide

(Table 1: Compound 2)

(64-1) To a solution of the compound from Example 1, the process (1-2) (4.16 g, 20.0 mmol) in dichloromethane (30 ml) was added triethylamine (4.2 ml, 30.0 mmol) and then, was slowly added a solution of 4-nitrobenzoyl chloride (4.00 g, 21.6 mmol) in dichloromethane (10 ml), and the solution was stirred for 7 hours. To the solution was added saturated sodium bicarbonate aq., and the mixture was extracted with chloroform.

[0164]

The organic layer was washed with 1N hydrochloric acid, saturated sodium bicarbonate aq. and saturated brine; dried; and evaporated. The residue was washed with diisopropyl ether to give N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-nitrobenzamide (7.02 g, Yield: 98.3 %) as a light yellow solid.

1H NMR(270 MHz, CDCl3) δppm: 1.53(9H, s), 7.17-7.29(4H, m), 7.85(1H, br.d, J=7.3 Hz). 8.17(2H, d, J=8.8 Hz), 8.32(2H, d, J=8.8 Hz), 9.88(1H, br.s)

[0165]

(64-2) To a solution of the compound from the process (64-1) (6.00 g, 16.8 mmol) in THF (20 ml) and methanol (20 ml) was added 10 % Pd/C (wet, 0.6 g) in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. After cease of absorption of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated. To the residue were added diisopropyl ether and ethyl acetate, and the precipitated solid was

collected by filtration and dried to give N-[2-(N-tert-butoxycarbonylamino) phenyl]-4-aminobenzamide (4.74 g, Yield: 86.2 %) as a white solid.
1H NMR(270 MHz, DMSO-d6) δppm: 1.46(9H, s), 5.84(2H, s), 6.61(2H, d, J=8.8 Hz), 7.10-7.18(2H, m), 7.46-7.55(2H, m), 7.68(2H, d, J=8.8 Hz), 8.67(1H, s), 9.49(1H, s)
[0166]

(64-3) To a solution of 1.6 g of the compound from the process (64-2) (4.88 mmol) in dichloromethane (15 ml) were added 0.8 ml of pyridine (9.9 mmol) and 0.96 ml of phenylacetyl chloride (7.26 mmol), and the solution was stirred for one day. After completion of the reaction, water was added and the precipitated crystals were collected by filtration to give 1.66 g of N-[2-(N-tert-butoxycarbonylamino)phenyl]-4-(phenylacetylamino)benzamide (Yield: 76 %).
[0167]

(64-4) To a solution of 1 g of the compound from the process (64-3) (2.24 mmol) in acetonitrile (25 ml) was added 0.88 ml of iodotrimethylsilane (6.18 mmol) at room temperature, and the solution was stirred for 3 hours. After completion of the reaction, the solution was concentrated. The residue was recrystallized from methanol to give 0.29 g of N-(2-aminophenyl)-4-(phenylacetylamino)benzamide (38 %) as white crystals.
[0168]
mp: 232-237 ℃
1H NMR(270 MHz, DMSO-d6) δppm: 3.69(2H, s), 4.90(2H, s). 6.60(1H, t, J=7.35), 6.77(1H, d, J=7.35), 6.96(1H, t, J=7.35), 7.15(1H, d, J=7.35), 7.22-7.35(5H, m), 7.72(2H, d, J=8.80), 7.95(2H, d, J=8.80), 9.57(1H, s), 10.43(1H, s)
IR(KBr): 2937, 2764, 1660, 1598, 1506, 1459
[0169]

As described in Example 64, the compounds of Examples 65 to 76 were prepared, each of whose melting point (mp), 1H NMR data, IR data are shown below.

Example 65

N-(2-aminophenyl)-4-(4-phenylbutanoyl)aminomethylbenzamide
(Table 1: Compound 4)
1H NMR(270 MHz, DMSO-d6) δppm: 1.91(2H, hep, J=7.3 Hz), 2.37(2H, t,

J=7.3 Hz), 2.64(2H, t, J=7.3 Hz), 5.0(2H, br.s), 6.61(1H, t, 7Hz), 6.79(1H, dd, J=1.5, 8.1Hz), 6.97(1H, t, J=7 Hz), 7.1-7.4(6H,m), 7.71(2H, d, J=8.8 Hz), 7.94(2H, d, J=8.8 Hz), 9.57(1H, s), 10.15(1H, s)

IR(KBr)cm-1; 3344, 1687, 1603, 1542, 1460, 1315, 1033, 842, 737

[0170]

Example 66

N-(2-aminophenyl)-4-[(4-chlorophenylacetyl)amino]benzamide (Table 1: Compound 15)

mp:>250 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.72(2H, s), 7.29-7.43(8H, m), 7.77(2H, d, J=8.8), 8.00(2H, d, J=8.80), 10.29(1H, s), 10.52(1H, s)

IR(KBr)cm-1: 3300, 2868, 1664, 1638, 1520

[0171]

Example 67

N-(2-aminophenyl)-4-[(2-nitrophenylacetyl)amino]benzamide hydrochloride (Table 1: hydrochloride of Compound 19)

mp: >250℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.20(2H, s), 7.20-7.30(3H, m), 7.40-7.45(1H, m), 7.60(2H, d), 7.71-7.77(3H, m), 8.02-8.10(4H, m), 10.27(1H, br.s), 10.64(1H,br.s)

IR(KBr)cm-1: 3263, 1676, 1647, 1518, 1184, 759

[0172]

Example 68

N-(2-aminophenyl)-4-[(4-nitrophenylacetyl)amino]benzamide (Table 1: Compound 21)

mp: 222-226 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.90(2H, s), 4.96(2H, br.s), 6.60(1H, dt, J=1.47, 6.61), 6.78(1H, dd, J=1.47, 6.61), 6.97(1H, dt, J=1.47, 6.61), 7.15(1H, dd, J=1.47, 6.61), 7.63(2H, d, J=8.80), 7.71(2H, d, J=8.80), 7.95(2H, d, J=8.80), 8.22(2H, d, J=8.80), 9.59(1H, s), 10.54(1H, s).

IR(KBr)cm-1: 3395, 3334, 1671, 1630, 1519, 1346

[0173]

Example 69

N-(2-aminophenyl)-4-[(2-aminophenylacetyl)amino]benzamide (Table

1: Compound 22)

mp: 177-182 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 3.54(2H, s), 4.88(2H, br.s), 5.09(2H, br.s), 6.55(1H, dd, 6.6, 7.3), 6.59(1H, dd, 7.3, 7.3), 6.68(1H, d, 7.3), 6.78(1H, d, 7.3), 6.96(2H, dd, 7.3, 7.3), 7.06(1H, d, 6.6), 7.15(1H, d, 7.3), 7.71(2H, d, 8.8), 7.95(2H, d, 8.8), 9.57(1H, br.s), 10.39(1H, br.s)

IR(KBr)cm-1: 3374, 3256(br.), 1683, 1597, 1503, 1317, 1262, 1180, 1153, 747

[0174]

Example 70

N-(2-aminophenyl)-4-[(4-aminophenylacetyl)amino]benzamide (Table 1: Compound 26)

mp: 219-226 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δppm: 3.46(2H, s), 4.93(4H, br.s), 6.52(2H,d, J=8.07), 6.59(1H, dt, J=1.47, 7.34), 6.77(1H, dd, J=1.47, 7.35), 6.97(1H, dt, J=1.47, 7.35), 6.99(2H, d, J=8.07), 7.15(1H, dd, J=1.47, 7.35), 7.70(2H, d, J=8.80), 7.93(2H, d, J=8.80)

IR(KBr)cm-1: 3278, 3032, 1675, 1628, 1516

[0175]

Example 71

N-(2-aminophenyl)-4-[(4-methoxyphenylacetyl)amino]benzamide (Table 1: Compound 32)

mp: >250℃

1H NMR(270 MHz, DMSO-d6) δppm: 3.62(2H, s), 3.74(3H, s), 6.90(2H, d, J=8.80), 7.26(2H, d, J=8.80), 7.30(3H, m), 7.39(1H, m), 7.77(2H, d, J=8.80), 7.99(2H, d, J=8.80), 10.26(1H, s), 10.44(1H, s)

IR(KBr)cm-1: 3300, 2759, 1670, 1638, 1514, 1250

[0176]

Example 72

N-(2-aminophenyl)-4-[(4-(N,N-dimethylamino)phenylacetyl)amino]benzamide (Table 1: Compound 157)

mp: 140 ℃

1H NMR(270 MHz, DMSO-d6) δppm: 3.04(6H, s), 3.67(2H, s), 7.16(2H, d, J=8.08), 7.29-7.40(6H, m), 7.76(2H, d, J=8.80), 7.99(2H, d, J=8.80), 10.29(1H, s), 10.47(1H, s)

IR(KBr)cm-1: 3244, 2951, 2639, 1647, 1599, 1507

[0177]

Example 73

N-(2-aminophenyl)-4-[(4-trifluoromethylphenylacetyl)amino]benzamide (Table 1: Compound 43)

mp: >250℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.84(2H, s), 6.89(1H, t, J=7.35), 7.00(1H, d, J=7.35 Hz), 7.11(1H, t, J=7.35), 7.25(1H, d, J=7.35), 7.57(2H, d, J=8.80), 7.71(2H, d, J=8.80), 7.73(2H, d, J=8.80), 7.97(2H, d, J=8.80), 9.87(1H, s), 10.54(1H, s)

IR(KBr)cm-1: 3260, 1664, 1605, 1521, 1327, 1119

[0178]

Example 74

N-(2-aminophenyl)-4-[(pyridin-2-yl)acetoamino]benzamide dihydrochloride(Table 1: hydrochloride of Compound 54)

mp: 154-175℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.60(2H, s), 7.30-7.46(3H, m), 7.56(1H, d, J=7.35), 7.79(2H, d, J=8.80), 7.95(1H, t, J=6.61), 8.01(1H, d, J=7.35), 8.11(2H, d, J=8.80), 8.49(1H, t, J=7.35), 8.87(1H, d, J=5.14), 10.46(1H, s)

[0179]

Example 75

N-(2-aminophenyl)-4-[(pyridin-3-yl)acetoamino]benzamide dihydrochloride(Table 1: hydrochloride of Compound 68)

mp: 182-189 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.12(2H, s), 7.29-7.59(4H, m), 7.80(2H, d, J=8.80), 8.05(1H, m), 8.11(2H, d, J=8.80), 8.57(1H, d, J=8.08), 8.85(1H, d, J=5.15), 8.95(1H, s), 10.25(1H, s), 10.48(1H, s)

[0180]

Example 76

N-(2-aminophenyl)-4-[(3-(pyridin-3-yl)propanoyl)amino]benzamide (Table 1: Compound 69)

mp: 184-186 ℃

1H NMR(270 MHz, DMSO-d6) δ ppm: 2.80(2H, t, J=7.34), 3.08(2H, t, J=7.34), 6.87(1H, t, J=8.07), 6.99(1H, dd, J=1.47, 8.07), 7.11(1H, dt, J=1.47, 8.07),

7.25(1H, d, J=8.07), 7.70(2H, d, J=8.80), 7.77(1H, dd, J=5.87, 8.07), 7.96(2H, d, J=8.80), 8.22(1H, d, J=8.07), 8.75(1H, d, J=1.47), 9.83(1H, s), 10.25(1H, s)

[0181]

Example 77

Preparation of N-(2-aminophenyl)-4-(N-benzylamino) carbonylbenzamide (Table 1: Compound 8)

(77-1) To a suspension of monomethyl terephthalate (13.0 g, 72.2 mmol) in toluene (100 ml) was added dropwise thionyl chloride (10 ml) at room temperature. After stirring at 80 ℃ for 3 hours, the solvent and an excess amount of thionyl chloride were removed by evaporation. The residue was suspended in dioxane (100 ml), and 2-nitroaniline (9.98 g, 72.2 mmol) were added to the suspension, followed by refluxing with heating for 4 hours.

[0182]

After cooling and evaporation, the residue was washed with methanol to give N-(2-nitrophenyl)-4-methoxycarbonylbenzamide (20.3 g, Yield: 93.7 %) as a yellow solid.

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.91(3H, s), 7.43-7.49(1H, m), 7.76-7.78(2H, m), 8.03(1H, d, J=8.1), 8.08(2H, d, J=8.8 Hz), 8.14(2H, d, J=8.8 Hz), 10.94(1H, s)

[0183]

(77-2) To a solution of the compound (4.24 g, 14.12 mmol) from the process (77-1) in THF (50 ml) and methanol (50 ml) was added 10 % Pd/C (0.4 g) in a stream of nitrogen, and the mixture was stirred in a stream of hydrogen for 1.5 hours. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with methanol to give N-(2-aminophenyl)-4-methoxycarbonylbenzamide (3.4 g, Yield: 87.5 %) as a light yellow solid.

1H NMR(270 MHz, DMSO-d6) δ ppm: 3.90(3H, s), 4.95(2H, s), 6.60(1H, dd, J=7.3, 8.1), 6.78(1H, d, J=7.3), 6.99(1H, dd, J=7.3, 7.3), 7.17(1H, d, J=7.3), 8.08(2H, d, J=8.1), 8.11(2H, d, J=8.1), 9.85(1H, s)

[0184]

(77-3) To a solution of the compound from the process (77-2) (2.71 g, 10.0 mmol) in dioxane (100 ml) and water (50 ml) was added 5 % sodium hydroxide aq. under ice-cooling, and then were added dropwise di-tert-butyl

dicarbonate (2.62 g, 12.0 mmol) in dioxane (40 ml). The mixture was stirred at room temperature for 4 hours and left overnight. To the mixture were added saturated brine and ethyl acetate, and the two layers were separated. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with methanol to give N-[2-(N-tert-butoxycarbonyl)amino]phenyl -4-methoxycarbonylbenzamide (3.54 g, Yield: 95.7 %) as a light brown solid.
1H NMR(270 MHz, DMSO-d6) δ ppm: 1.44(9H, s), 3.90(3H, s), 7.12-7.24(2H, m), 7.55-7.58(2H, m), 8.09(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.72(1H, s), 10.00(1H, s)

[0185]

(77-4) A suspension of the compound from the process (77-3) (3.00 g, 8.10 mmol) in methanol (50 ml) and 0.5N lithium hydroxide aq. (25 ml) was heated with stirring at 40 ℃ for 5 hours. After removing methanol by evaporation, to the residue was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with a small amount of water and saturated brine, dried and evaporated. The residue was washed with methanol to give terephthalic mono-2-(N-tert-butoxycarbonyl) aminoanilide (2.24 g, Yield: 77.6 %) as a light brown solid.
1H NMR(270 MHz, DMSO-d6) δ ppm: 1.45(9H, s), 7.12-7.21(2H, m), 7.53-7.58(2H, m), 8.06(2H, d, J=8.8 Hz), 8.10(2H, d, J=8.8 Hz), 8.71(1H, s), 9.97(1H, s)

[0186]

(77-5) To a suspension of the compound from the process (77-4) (0.20 g, 0.56 mmol) in dichloromethane (4 ml) were added benzylamine (0.14 g, 1.3 mmol) and then triethylamine (0.21 ml, 1.5 mmol). To the solution was added 0.25 g of 2-chloro-1,3-dimethylimidazolium chloride (1.48 mmol) under ice-cooling, and then the mixture was stirred under ice-cooling for an hour and at room temperature for an hour. After diluting with chloroform and adding water, the aqueous layer was extracted with chloroform.

[0187]

The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography on silica gel (eluent: chloroform:methanol = 10:1). The solid obtained was washed with

diethyl ether to give N-(2-tert-butoxycarbonylaminophenyl)-4-(N-benzylamino)carbonylbenzamide (279 mg, Yield: 62.6 %) as a white solid.
1H NMR(270 MHz, DMSO-d6) δ ppm: 1.45(9H, s), 4.52(2H, d, J=5.8 Hz), 7.13-7.28 (4H, m), 7.34-7.35(3H, m), 7.56(2H, d, J=8.1 Hz), 8.05(4H, s), 8.71(1H, br.s), 9.23(1H, t), 9.94(1H, s)

[0188]

(77-6) To the compound from the process (77-5) (151 mg, 0.339 mmol) was added 4N hydrochloric acid-dioxane (5 ml) at room temperature, and the mixture was stirred for 4 hours. After evaporation, the mixture was partitioned between ethyl acetate and saturated sodium bicarbonate aq. After removing the precipitate, the aqueous layer was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. To the residue was added diethyl ether, and the precipitate was collected by filtration and dried to give N-(2-aminophenyl)-4-(N-benzylamino) carbonylbenzamide (78 mg, 67 %) as a white solid.
mp: 239-241 ℃(dec.)
1H NMR(270 MHz, DMSO-d6) δ ppm: 4.51(2H, s), 4.93(2H, br.d), 6.60(1H, dd, J=7.3, 7.3 Hz), 6.78(1H, d, J=8.1 Hz), 6.95(1H, dd, J=7.3, 8.3 Hz), 7.18(1H, d), 7.23-7.35(5H, m), 8.01, 8.07 (4H, d, J=8.8 Hz), 9.22(1H, br.t), 9.81(1H, br.s)

[0189]

As described in Example 77, the compound of Example 78 was prepared, whose melting point (mp), 1H NMR data, IR data are shown below.

[0190]

Example 78

N-(2-aminophenyl)-4-[N-(2-phenylethyl)amino]carbonylbenzamide (Table 1: Compound 9)
mp: 237-240 ℃(dec.)
1H NMR(270 MHz, DMSO-d6) δ ppm: 2.87(2H, t, 7.3), 3.51(2H, dt, 5.9, 7.3), 4.94(2H,br.s), 6.60(1H, dd, 7.3, 7.3), 6.78(1H, d, 7.3), 6.98(1H, dd, 7.3, 7.3), 7.15-7.34(6H, m), 7.93(2H, d, 8.1), 8.04(2H, d, 8.1), 8.73(1H, t, 5.1), 9.76(1H, br.s)
IR(KBr)cm-1: 3396, 3320, 1625, 1602, 1539, 1458, 1313, 699

[0191]

Example 79

Preparation of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)amino] benzamide (Table 1: Compound 158)

(79-1) To a solution of 3 g of the compound from Example 64, the process (64-2) (9.2 mmol) and 2.16 g of 4-nitrophenoxyacetic acid (11.0 mmol) in DMF (7 ml) were added 2.82 g of dicyclohexylcarbodiimide (13.8 mmol) in DMF (5 ml) and a catalytic amount of N,N-dimethylaminopyridine, and the mixture was stirred for one day. After completion of the reaction, ethyl acetate was added to the mixture, insolubles were filtered out through celite, and the solvent was removed by evaporation.

[0192]

The residue was recrystallized from chloroform to give 2.34 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-nitrophenoxyacetyl)amino]benz amide (Yield: 50 %).

1H NMR(270 MHz, DMSO-d6) δ ppm: 1.45(9H, s), 4.97(2H, s), 7.12-7.26(3H, m), 7.23(2H, d, J=8.80), 7.53(1H, dt, J=2.20, 7.35), 7.79(2H, d, J=8.80), 7.95(2H, d, J=8.80), 8.25(2H, d, J=8.80), 8.71(1H, s), 9.79(1H, s), 10.52(1H, s)

[0193]

(79-2) To a solution of 0.7 g of the compound from the process (79-1) (1.38 mmol) in acetonitrile (10 ml) was added 1.26 ml of iodotrimethylsilane (8.85 mmol) at room temperature, and the solution was stirred for 2 hours. After completion of the reaction, the solution was concentrated and ethyl acetate was added. The solution was stirred for 20 min, and the precipitated crystals were collected by filtration. The crystals were dissolved in methyl ethyl ketone. The solution was washed with saturated sodium thiosulfate aq. and saturated brine in sequence, dried out with anhydrous magnesium sulfate, and evaporated. The residue was washed with ethyl acetate to give 0.22 g of N-(2-aminophenyl)-4-[N-(4-nitrophenoxyacetyl)
amino]benzamide (Yield: 39 %) as white crystals.

mp: 212-215 ℃(dec.)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.97(2H, s), 6.88(1H, t, J=7.35), 6.99(1H, d, J=7.35), 7.11(1H, t, J=7.35), 7.23(2H,d, J=8.80), 7.24(1H, 1H, m), 7.77(2H, d, J=8.80), 8.00(2H, d, J=8.80), 8.25(2H, d, J=8.80), 9.89(1H, s), 10.52(1H, s)

IR(KBr)cm-1: 3382, 3109, 1650, 1591, 1508, 1341

[0194]

Example 80

Preparation of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl) amino]benzamide (Table 1: Compound 159)

To a solution of 1.41 g of the compound from Example 79, the process (79-1) (2.78 mmol) in methanol (15 ml) and THF (25 ml) was added 10 % Pd-C, and the mixture was stirred in an atmosphere of hydrogen, at room temperature for an hour. After completion of the reaction, the catalyst was filtered out and the filtrate was concentrated. The residue was triturated with diisopropyl ether to give 1.1 g of N-[2-(tert-butoxycarbonylamino)phenyl]-4-[(4-aminophenoxyacetyl)amino]benzamide.

[0195]

The product was dissolved in 15 ml of acetonitrile. To the solution was added 0.74 ml of iodotrimethylsilane (5.20 mmol), and the mixture was stirred at room temperature for 3 hours. After completion of the reaction, the mixture was evaporated. The residue was washed with methyl ethyl ketone to give 0.86 g of N-(2-aminophenyl)-4-[(4-aminophenoxyacetyl)amino]benzamide (Yield: 83 %).

mp: (amorphous)

1H NMR(270 MHz, DMSO-d6) δ ppm: 4.82(2H, s), 7.13(2H, d, J=8.80), 7.30-7.48 (6H, m), 7.82(2H, d, J=8.80), 8.03(2H, d, J=8.80), 10.34(1H, s), 10.46(1H, s)

IR(KBr)cm-1: 2873, 2590, 1680, 1602, 1505, 1243

[0196]

Pharmacological test example 1

Test for induction of differentiation in A2780 cells

Increase of alkaline phosphatase (ALP) activity is known as an indicator for differentiation of human colon cancer cells. For example, it is known that sodium butylate may increase ALP activity (Young et al., Cancer Res., 45, 2976(1985); Morita et al., Cancer Res., 42, 4540(1982)). Thus, differentiation inducing action was evaluated using ALP activity as an indicator.

[0197]

(Experimental procedure)

To each well of a 96-well plate was inoculated 0.1 ml of A2780 cells (15,000 cells/well) and on the next day was added 0.1 ml of a stepwise diluted test compound solution with the medium. After incubation for 3 days, the cells on the plate were washed twice with a TBS buffer (20 mM Tris, 137 mM NaCl, pH 7.6). Then, to each well was added 0.05 ml of 0.6 mg/ml p-nitrophenylphosphate (9.6 % diethanolamine, 0.5 mM $MgCl_2$ (pH 9.6)) solution, and the plate was incubated at room temperature for 30 min. The reaction was quenched with 0.05 ml/well of 3N sodium hydroxide aq. For each well, an absorbance at 405 nm was measured to determine the minimum concentration of the drug inducing elevation of ALP activity (ALPmin).

(Experimental Results)

The results are shown in Table 2.

[0198]

Table 2: Effect for induction of differentiation in A2780 cells

Test Compound	ALPmin(μM)
Compound in Example 4	1
Compound in Example 5	1
Compound in Example 8	1
Compound in Example 9	1
Compound in Example 10	3
Compound in Example 11	1
Compound in Example 13	1
Compound in Example 15	3
Compound in Example 16	3
Compound in Example 18	3
Compound in Example 23	1
Compound in Example 24	1
Compound in Example 25	3
Compound in Example 26	1
Compound in Example 27	10
Compound in Example 28	10
Compound in Example 29	10
Compound in Example 30	0.1
Compound in Example 31	0.1
Compound in Example 32	0.1
Compound in Example 33	1
Compound in Example 34	1
Compound in Example 35	1
Compound in Example 36	3
Compound in Example 37	3
Compound in Example 38	1
Compound in Example 39	1
Compound in Example 40	3
Compound in Example 41	3
Compound in Example 42	3
Compound in Example 43	3

Compound in Example 44	3
Compound in Example 47	3
Compound in Example 48	3
Compound in Example 49	3
Compound in Example 50	3
Compound in Example 51	3
Compound in Example 52	3
Compound in Example 53	30
Compound in Example 54	0.1
Compound in Example 55	0.3
Compound in Example 56	3
Compound in Example 57	0.1
Compound in Example 58	3
Compound in Example 59	3
Compound in Example 60	10
Compound in Example 61	0.1
Compound in Example 62	0.1
Compound in Example 63	3
Compound in Example 64	1
Compound in Example 66	3
Compound in Example 68	1
Compound in Example 70	1
Compound in Example 71	1
Compound in Example 72	3
Compound in Example 73	1
Compound in Example 74	3
Compound in Example 75	3
Compound in Example 76	0.1

[0199]

Pharmacological test example 2

Antitumor action test

(Experimental procedure)

To a nude mouse was inoculated tumor cells subcutaneously subcultured in a nude mouse (HT-29, KB-3-1). When the volume became about

20 to 100 mm^3 and take was confirmed, administration of a drug was initiated. This day was Day 1, and subsequently the drug was orally administered in Day 1 to 5, in Day 8 to 12, Day 15 to 19 and in Day 22 to 26.

The volume of the tumor was determined from the following equation:

(Volume of a tumor) = 1/2 x (major axis) x (minor axis)^2

(Experimental Results)

The results for the compound of Example 32 (dose: 66 μ mol/kg) against HT-29 are shown in Figure 1.

[0201]

The results for the compound of Example 32 (dose: 66 μ mol/kg) against KB-3-1 are shown in Figure 2.

[Effects of the Invention]

The novel benzamide edrivative of the present invention has differenciation-inducing effect and is useful for medical and pharmaceutical products. In particular, it has high effect as an anticancer drug, is effective against hematologic malignancy and solid tumors.

[Brief Description of the Drawings]

[Fig.1]

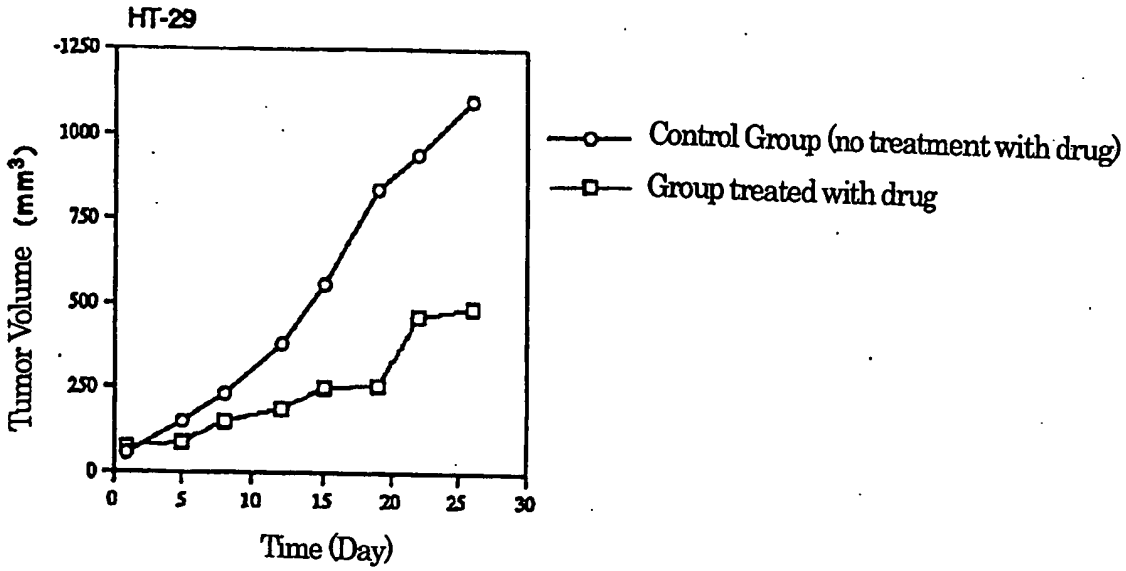
It shows a change of the volume of the tumor when the compound of Example 32 was administered against the tumor cell HT-29.

[Fing.2]

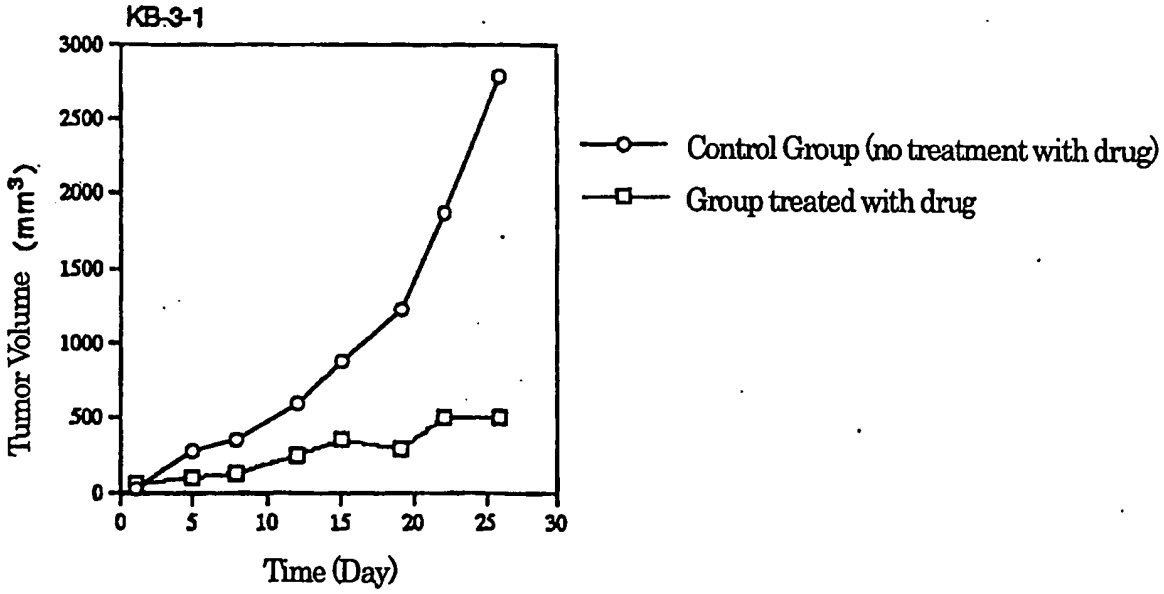
It shows a change of the volume of the tumor when the compound of Example 32 was administered against the tumor cell KB-3-1.

[Document Name] Drawing

[Figure 1]



【図２】

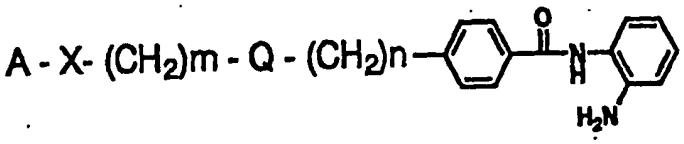


[Document Name] Abstract

[Abstract]

[Object] To provide a novel benzamide derivative having differenciation-inducing effect.

[Means for solution] A novel bexamide derivative represented by the general formula (1):



(1)

[Effect] Since the novel benzamide derivative represented by the general formula (1) has differenciation effect, it is useful for therapeutic and inporoving agent malignant tumors, autoimmune diseases and dermatologic diseases. In particular, it has high effect as an anticancer drug, is effective against hematologic malignancy and solid tumors.